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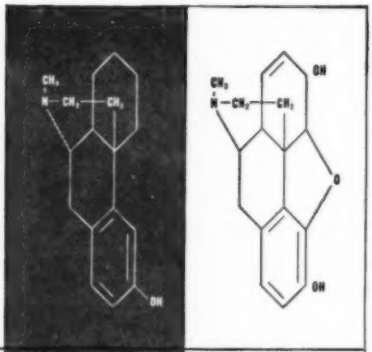

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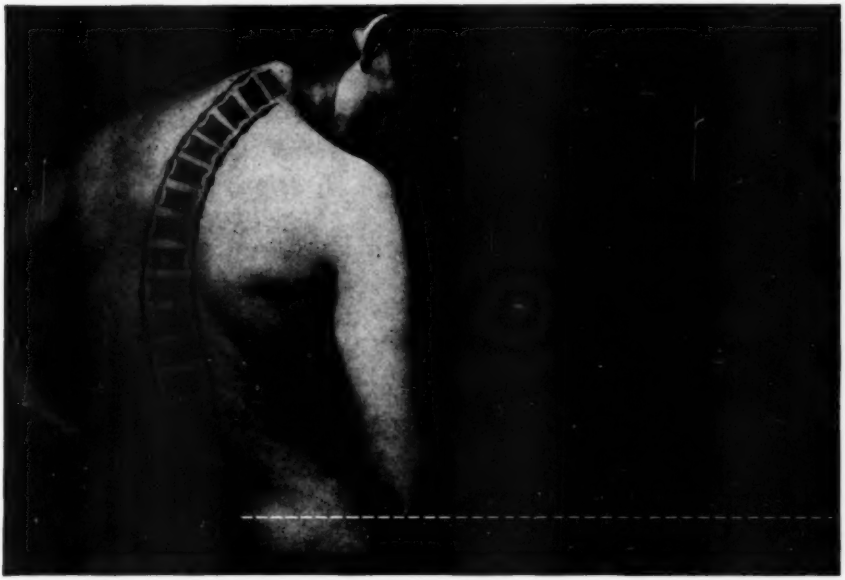

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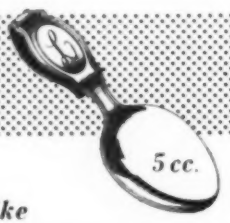

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 28, NO. 10 OCTOBER 1952

ON EXTRACORPOREAL DIALYSIS OF BLOOD IN ACUTE ANURIA. THE IMPORTANCE OF β-OXIDATION IN THE KIDNEY TUBULES*

I. SNAPPER

THERE are many reasons why efforts to prolong the life of uremic and especially of anuric patients by extracorporeal dialysis of blood have attracted general attention. Autopsies of patients with anuria after burial under debris during the bombardment of London have shown that this condition was due to necrosis of the renal tubules—that is, of the epithelial part of the nephron, whereas the glomeruli were intact.[1] In general, necrosis of epithelial tissue is followed by complete regeneration. Thus, unless there is complete disruption of the renal structure,[2] acute anuria due to necrosis of the tubules is a reversible process. It has gradually transpired that many other instances of acute anuria—due to shock, incompatible blood transfusion, sulfa poisoning, hepato-renal syndrome, etc.—were also caused by damage to the tubules and not by obstruction of the tubules. The following explanation of the anuria seems a plausible one. As soon as the wall of the tubule dies, the tubular epithelium is transformed into a non-specific dialyzing membrane. Then the colloid

* From the Second Medical Service of the Mount Sinai Hospital, New York, N. Y. Presented December 18, 1951, before the Section on Medicine of The New York Academy of Medicine.

osmotic pressure of the blood plasma draws the water from the tubules towards the lumen of the tubular blood vessels and acute anuria results. In such cases, depressed renal blood flow must also be an important factor in the production of anuria.

In these cases the treatment must be aimed toward obtaining a survival period of more than twelve days after the beginning of the anuria. After a period of four days, regeneration of the tubules sets in and after about ten days urine secretion starts anew. As a matter of fact, the greater part of the patients who survived the anuric episode for more than ten or twelve days did recover.[3] Dialysis of blood which leads to the removal of many poisonous substances retained in the plasma must be one of the methods by which life can be prolonged.

Extracorporeal dialysis of blood of humans during life has for a long time been a dream of the experimental physiologists. Abel[4] in 1913 dialyzed blood of living animals. Haas, Necheles, Thalhimer and others improved Abel's technique until in 1943, Kolff[5] constructed an apparatus in which dialysis of blood of the living human patient could actually be performed. It is imperative to follow closely the change of the blood electrolytes occurring during dialysis. The introduction of the flame photometer which facilitates the rapid determination of the blood electrolytes has been a major factor in reducing the dangers of extracorporeal dialysis. The ideal goal of the experimentalists consists of restoration of the composition of the extracellular fluid of the anuric patient to normal. Here considerable caution is necessary.

During renal insufficiency, whether caused by glomerulonephritis or acute necrosis of the tubular apparatus, the sodium of the serum is low normal; chlorides, CO_2-combining power, and calcium are considerably decreased; urea, uric acid, creatinine, potassium, phosphates, and aromatic oxy-acids are increased. It seems at least doubtful whether it is advisable to try to increase the chlorides of the serum of uremic patients to normal values. Efforts to raise the chloride content of the serum during uremia have always had catastrophic results and thus attempts at restoration of homeostasis in uremia require great caution. At the same time it is highly questionable whether the increase of blood urea, uric acid and creatinine actually threatens life; the retention of these waste products is probably not of great clinical importance. The increase of the urea content of the serum may even have a diuretic effect. Thus the clinical efficacy of a method such as dialysis cannot be judged merely

by the large amounts of urea which are removed from the blood during the dialyzing period. This may well be unimportant as far as survival of the patient is concerned. It is certain that the accumulation of at least two dialyzable substances in the blood of the anuric patient—that is, of potassium and of inorganic and aromatic acids, threatens life. Since these substances are dialyzable, they can easily be removed by extracorporeal dialysis. For the time being, we should not be over ambitious. In most cases we should be satisfied to improve the condition of anuric patients by the removal of these two toxic substances and should not always strive for restoration of homeostasis of the plasma. In order to prevent heart failure, it may be necessary to remove part of the extracellular fluid during the dialysis. This requires very careful adjustment of the osmotic pressure of the dialyzing fluid and continuous checking of osmotic pressure and electrolyte content of the serum of the patient.

Since accumulation of potassium and acids is so important in determining the ultimate prognosis of acute anuria, it should be our aim to reduce the formation of these substances during the anuria as much as possible. During the oliguric and anuric phase the amount of fluid given to the patient should be restricted. Unless fluid is lost by vomiting or by diarrhea, the fluid intake should not exceed 800 cc. or maximally 1000 cc. and this fluid should not contain potassium. Fruit juice is high in potassium. Therefore no orange juice should be given to these patients, but this popular drink should be replaced by sugar water or weak tea with sugar. It is generally accepted that if only fluid and no calories are given during the anuria, protein of body cells will be used to provide calories. Destruction of cells will take place and potassium will be released. In order not to increase the hyperpotassemia inordinately, it seems advisable to administer calories during the anuric stage. The calory-providing food should be chosen in such a way that no substances are formed which would burden the function of the damaged kidney.

Borst[6] has advised feeding the anuric patient with butter and sugar. For this purpose 200 grams of ground sugar are suspended in 200 grams of melted butter and about 12 grams of flour and coffee flavor are added. This mixture is put into the icebox and is then divided into small butter-sugar balls. It has been difficult in practice to persuade patients to swallow these unsavory butter balls. More popular is the treatment advocated by Bull.[7] A mixture of 400 grams of glucose and 100 grams of peanut oil is emulsified with acacia gum and diluted with water to 1 liter. This

emulsion is given daily by continuous intragastric drip via a plastic intranasal tube 2-3 millimeters in diameter. Not every patient tolerates this mixture. It also has caused vomiting and diarrhea.

It is advisable to remove potassium from the plasma in the course of the anuria, even before a considerable degree of hyperpotassemia has been reached and before changes in the electrocardiogram can be discovered. Potassium can be removed by lavage of the small intestine.[8] Kelley and his associates[9] have placed a Levine tube in the stomach and a Miller-Abbott tube in the jejunum. In the course of twenty-four hours 4 liters of a solution containing 0.6 per cent Na Cl, 0.3 per cent $NaHCO_3$, 0.01 per cent calcium gluconate and 2 per cent of glucose are introduced via the Levine tube and sucked out via the Miller-Abbott tube. By this lavage large amounts of potassium can be removed within a few hours. This method is so effective that every few hours the potassium content of the serum must be determined in order to prevent dangerous hypopotassemia. The acidosis which develops during anuria can be combated by intravenous injections of 5 per cent sodium bicarbonate. Here caution is necessary because of the danger of pulmonary edema. Since anemia interferes with the function of the kidney, transfusions of packed cells are helpful. The amounts of sodium citrate introduced with the red cells may have a beneficial effect upon the acidosis. It must be added that the handling of patients who develop anuria after an operation is much more complicated. It is difficult to estimate exactly how much extra fluid and salts the postoperative condition of these patients requires. Comparable difficulties are encountered when the anuric patient develops fever.

Careful conservative treatment of acute anuria will often keep the patients in good condition for more than ten days. Usually spontaneous urinary secretion sets in before extracorporeal dialysis becomes necessary and it is generally estimated that about 85 per cent of the cases with acute anuria clear up with conservative treatment. Only exceptionally tenacious cases of anuria will require extracorporeal dialysis. The same holds true for patients whose treatment during the initial period of anuria has been unsatisfactory.

The beneficial effect of extracorporeal dialysis consists only of the removal of small molecular substances from the blood. It is at best an artificial apparatus substituting for the ultrafiltration which takes place at the level of the glomeruli and for the transportation of these substances through the tubular lumen. The function of the kidney, how-

ever, is much more complicated. Not only do the tubular cells actively secrete large molecules from the blood to the tubular lumen, they also reabsorb colloid substances like proteins, cholesterol, etc. In addition, non-excretory functions such as synthesis and specific oxidations are carried out in kidney cells. The following paragraphs will serve to underline the difference between the actual functions of the kidney and the extracorporeal dialysis.

1. Recently it has been emphasized that complex enzymatic systems located in the cells of the tubules play an important role in the function of the kidney.[10] In order to reabsorb substances from the lumen of the tubule against a gradient into the blood, energy is necessary. The same holds true for the transport of large molecules from the blood to the tubular lumen. The energy required for tubular reabsorption and secretion is obtained by the same enzymatic processes which render muscular contraction and propagation of nerve impulses possible,—that is, by the utilization of the energy present in certain phosphate bonds. For this purpose adenylic acid and inorganic phosphates are conjugated in the tubular cells by aerobic phosphorylation until adenosine triphosphate results. The potential energy present in the phosphate bonds of the latter substance is liberated by phosphatase activity and used for the reabsorption, secretion and synthesis performed by the tubular cells. When aerobic phosphorylation is inhibited by administration of certain substances, such as dinitrophenol, the transportation of phenolred, diodrast, and also of para-aminohippuric acid from the blood to the tubular lumen is inhibited. In this way the metabolic functions of the tubular cells have been closely linked to the excretory and secretory functions of the nephrons.

These modern conceptions have revived the interest in metabolic, non-excretory functions of the kidney. Whereas the production of energy by the enzymatic processes occurring in renal cells follows the common pattern of phosphorylation as present in the cells of many different organs, the kidney is also capable of performing more specific syntheses and oxidations.

2. It is superfluous to stress the importance of the formation of ammonia in the kidney. Classical experiments have proved that the ammonia excreted in the urine is produced in the kidney tubule by degradation of glutamine under influence of glutaminase to glutamic acid and ammonia. The latter substance is also formed by the action of an

α-amino-oxydase on certain amino acids.[11] When acidosis sets in, the amount of ammonia produced increases rapidly. Since the ammonia formation permits neutralization and excretion of acid without loss of large amounts of fixed base, ammonia production by the kidney is one of the principal mechanisms by which the deleterious influence of acidosis is minimized.

3. The kidney can synthesize hippuric acid from benzoic acid and glycin. It also synthesizes phenaceturic acid from phenylacetic acid and glycin.

The synthesis of hippuric acid takes place in the intact kidney if the organ is perfused with blood, containing sodium benzoate. During perfusion of the intact kidney with plasma or saline and sodium benzoate, this synthesis does not occur. The same holds true when suspensions of renal cells are used. Thus there are certain functions of the intact kidney that cannot be accomplished by suspensions of kidney cells.

4. By perfusion of the isolated kidney with blood containing aromatic fatty acids, it can be shown that the kidney performs the following oxidation's.[10] Phenylpropionic acid ($C_6H_5CH_2\ CH_2\ COOH$) to benzoic acid (C_6H_5COOH). Phenylbutyric acid ($C_6H_5\ CH_2\ CH_2\ CH_2\ COOH$) to phenylacetic acid ($C_6H_5\ CH_2\ COOH$). Phenylvalerianic acid ($C_6H_5\ CH_2\ CH_2\ CH_2\ CH_2\ COOH$) to benzoic acid. Phenylcapronic acid ($C_6H_5\ CH_2\ CH_2\ CH_2\ CH_2\ CH_2\ COOH$) to phenylacetic acid.

The latter two oxidations consist of two consecutive β-oxidations.

In the liver an incomplete β-oxidation of fatty acids and of amino acids to diacetic acid, and β-hydroxybutyric acid takes place. The liver, however, does not oxidize either of these substances. The kidneys —and incidentally, also the muscles—complete this partial β-oxidation and during perfusion of the intact kidney large amounts of both these so-called ketone bodies disappear.[12]

It is interesting that acetate which must be liberated during the oxidations of aromatic fatty acids and of ketone bodies strongly increases the excretion of para-amino hippuric acid by the tubules. In this way β-oxidation by the kidney tubules does not only act as a detoxifying mechanism, but at the same time it favors the excretion of large molecules by these tubules.

It should be stressed that β-oxidations in kidneys of different species are not always the same. Whereas the isolated intact human kidney

easily oxidizes phenylpropionic acid to benzoic acid and excretes it in the urine as hippuric acid, the isolated kidney of the dog performs only a partial oxidation of phenylpropionic acid. During perfusion of the dog's kidney two H atoms are removed from the two CH_2 groups of the phenylpropionic acid, resulting in the formation of cinnamic acid (C_6H_5 CH = CH COOH). The latter substance then appears in the urine, excreted by the perfused kidney, in the form of cinnamoylglycin, but no hippuric acid is formed.[13]

It follows that when the kidney is diseased, or when the tubular apparatus is temporarily out of function, a syndrome must result which is due to—

the abolition of excretion of small molecular substances which under normal circumstances leave the kidney via glomeruli and are transported by the tubules;

the abolition of secretory processes and absorption of colloids by the tubules;

the abolition of synthesis and oxidation by the tubules. The absence of the latter processes may leave large amounts of toxic substances in the organism which under normal circumstances would have disappeared or been detoxified.

Extracorporeal dialysis at best replaces the excretion of small molecular substances which under normal circumstances are excreted by the glomeruli. It cannot replace either the tubular secretion or the synthesis and oxidations which under normal circumstances are performed by the kidney. The clinical syndrome of uremia does not depend only upon retention of substances which should have been excreted by the glomeruli and transported by the tubules. The dangers for life inherent in the absence of tubular secretion and of synthesis and oxidation by the kidney parenchyma should not be underestimated.

We know that retention of potassium and acids caused by the absence of the transport function of the kidney tubules threatens life. It is therefore a major advance that by the introduction of extracorporeal dialysis the dangers inherent in potassium and acid retention can be lessened. The detoxifying functions of the kidney which result from synthesis and oxidation and also from the function of tubular secretion are not replaced by extracorporeal dialysis. It thus seems advisable to avoid the designation "artificial kidney" for the apparatus in which the blood is dialyzed. Even if the dangers of hyperpotassemia and acidosis

have been overcome by dialysis, life may still be endangered by the abolition of the secretion of large molecules by the tubules and also by the products of insufficient renal synthesis and oxidation. This may well be the reason why exchange transfusion has proved to be helpful in the treatment of certain cases of acute anuria, although the quantities of small molecular substances removed by this method are negligible compared with the results of extracorporeal dialysis.[14]

Summary

Extracorporeal dialysis permits removal of small molecular substances from the blood. Use of the artificial kidney can improve the condition of patients with anuria by removal of potassium and acids. It is true that many other substances are also removed by extracorporeal dialysis, but, as far as is known, the other dialyzable compounds, retained in the blood during anuria, do not endanger life. Treatment of the anuric patient should consist of fluid restriction, possibly feeding with moderate amounts of sugar and fat, combating of acidosis by intravenous sodium bicarbonate injections and of hyperpotassemia by intestinal lavage. In the correctly treated patient with acute anuria, extracorporeal dialysis will only rarely be necessary.

It is emphasized that use of the artificial kidney at best only replaces the glomerular filtration but not the secretion of larger molecules by the tubules nor the conjugation and oxidation in the tubules. The importance of β-oxidation taking place in the tubular cells is emphasized. Since lack of detoxification and oxidation of toxic substances during anuria continues, successful removal of dialyzable toxic products by the use of the artificial kidney may not be sufficient to save the life of the uremic patient.

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The list of "Recent Accessions to the Library" which has hitherto been published in the *Bulletin of The New York Academy of Medicine* will cease to appear there hereafter. Instead, it will be issued in mimeographed form and will be available to Fellows of the Academy and to other libraries on request. Applications to be placed on its mailing-list should be made to the Librarian.

THE MANAGEMENT OF THE NEPHROTIC SYNDROME*

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THE ideal management of any disease process would be an attack on its cause. Failing that, if one could understand the pathogenesis of the process and interrupt it at a basic level, a great deal would be accomplished. If neither of these approaches is possible, one can at least try to modify the symptoms as they present.

The very fact that we are talking tonight about a "syndrome" implies that we are not at all sure that we are dealing with a single disease entity, even when we eliminate the nephrosis of amyloidosis, syphilis, etc., and so at present we cannot hope to know the cause. We are all painfully aware of the differences of opinion which exist with regard to the nature of the condition. It has been customary in the past to accept most examples of the nephrotic syndrome as merely a phase of chronic glomerulonephritis and to accord them a bad prognosis. But it has usually been acknowledged that an entity exists called "pure lipoid nephrosis" which is different from the former and which has a good prognosis. Lately there has been a growing opinion among many of us, especially pediatricians, that the nephrosis usually seen in childhood is one disease entity which may have variable effects on the kidney.[1] We would feel that whether the process progresses to renal failure or subsides depends upon the immeasurable factor of "host response." It is likely that there are different "trigger mechanisms" which set the whole process in motion, but once started the further development of the disease will depend on the individual's reaction to it. The fact that the condition as seen in adults looks different clinically and pathologically from its counterpart in children might mean that it is truly a different disease, or else that it is the result of altered host response. With our

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present knowledge, it is useless to speculate whether "nephrosis" is merely one phase of glomerulonephritis or whether it is a separate disease entity. It can only be said that there is no way of determining prognosis in an individual case by present attempts at classification.

As a pediatrician addressing a group of internists I should like to outline some of the features of the condition in childhood and compare them with those seen in adults. The onset is usually insidious without known preceding infection or signs of glomerulonephritis and occurs most frequently between one and three and one-half years of age. The usual duration is about two years, but there is great variation. Of all children presenting with the nephrotic syndrome about one-third progress to apparent complete recovery, two-thirds die with failing kidneys. Those who die, in contrast to adults, usually do so while still edematous, without hypertension and with only moderate azotemia. With modern antibacterial therapy death from infection is rare. At autopsy, in addition to the tubular involvement, the glomeruli show thickening of the basement membrane of the capillaries, some hyalinized glomeruli, a few crescents, and are usually diagnosed as "interstitial nephritis." Also the tubules are apt to be loaded with casts giving the impression that there may have been actual mechanical obstruction to urine flow. The children usually die while the kidney is still large, before reaching the contracted state so frequently seen in adults. In the contracted kidneys glomerular destruction is a very prominent feature. Thus clinically and morphologically there are such differences in the syndrome in the two age groups as to suggest that they may be different diseases.

Discussion of the management of such cases will be limited largely to attempts to relieve the most distressing symptom – anasarca. It has already become apparent that our knowledge is too weak to hope to attack the cause, and the pathogenesis of such phenomena as hypoproteinemia, proteinuria, hypercholosterolemia, etc., is so obscure that the only level where we seem able to approach the problem is most superficial. Certain aspects will be deliberately omitted because they are common to other conditions. Among these are the treatment of infection, the moral support of the patient and family, and the management of the failing kidney.

A list of treatments used in nephrosis is long and amusing, and will vary depending on the personal contacts of the individual making up the list, as many things which have been tried have never been pub-

lished. In a limited time, one cannot cover the whole field, but it is worth mentioning some of the types of treatment which have been used. The usual diuretics which have proven useful in cardiac edema have been found wanting in this condition. The xanthine derivatives have no appreciable effect. The mercurials may produce a transitory increase in urinary output, but have the objection, perhaps only theoretical, that they work by toxic action on a kidney already in a questionable state of health.

Dietary approaches also are discouraging. High and low protein diets have both been tried with no convincing evidence that either is effective. One group, postulating that a nephrotic might be unable to utilize foreign proteins, tried feeding human placenta to patients in an effort to make available homologous protein, without success. One gets the impression that the accumulation of edema is slower on a low salt diet, but real diuresis under these circumstances is rare. A truly no-salt diet may be more effective as is suggested by the claims for the Kempner rice diet,[2] but such a regimen in children may induce total anorexia which seems scarcely justifiable. There is the further concern that salt deficiency in itself may cause unfavorable results. This latter factor must be taken into account when considering the use of cation exchange resins in an attempt to remove sodium from a patient. Early reports suggest that these resins have not proved effective in relieving nephrotic edema.[3]

In contrast to the above approach is that of Osman[4] and later of Fox[5] where high sodium intakes were forced. Organic salts of sodium were used so that alkalinization was achieved and under these circumstances brisk diuresis has occurred frequently. But some of the patients so treated may increase their edema inexorably with a steady decrease in their extracellular fluid chlorides and severe alkalosis. Treatment, even when successful, is long, drawn out and should be carried out in a hospital. This approach has demonstrated, contrary to former belief, that diuresis can and does occur in the presence of a high sodium intake, but at present, though it deserves further exploration, it cannot now be considered as a practicable therapeutic method.

The various attempts to elevate plasma oncotic pressure have met with some success in inducing diuresis but in general such a remission has been short-lived. Concentrated salt-poor serum albumin is almost prohibitively expensive, but if enough of this material is given a tran-

sient delivery of edema can usually be induced. Other large molecule materials have been used with varying success. Acacia given intravenously frequently induced diuresis but unfortunately proved toxic and has been abandoned. Dextran, a large molecule polymer of simple sugars, has been reported on with enthusiasm from overseas, but preparations in this country have been pyrogenic so that it has not been widely used. More recently polyvinylpyrrolidone (PVP), another synthetic large molecule polymer, has been introduced into this country. Too little work has yet been done with it in nephrosis, but it may prove useful in inducing transient remissions of the edema.

The idea that relief might be obtained by the administration of various hormones is an old one. Thyroid extract was the earliest to be tried because the elevated cholesterol and lowered basal metabolic rate made it appear that there might be a thyroid deficiency. As with many agents tried, occasional diuresis was observed, but with the lapse of time it has become evident that such apparent success must have been coincidence; so this approach, too, has fallen into discard. The use of pitressin by McQuarrie[6] is of interest. By deliberately inducing antidiuresis with this substance for a few days he occasionally found a rebound diuresis following withdrawal which was greatly in excess of the fluid retained. In general, however, the results were not impressive enough for this to be adopted as a useful form of therapy. Other hormones such as testosterone and desoxycorticosterone have also been used without success. The hormonal approach most used currently will be discussed later.

That certain infectious diseases can induce remissions in the nephrotic syndrome seems well established now. Measles is the best documented of these; it would appear from reported figures and from our own experience that in about four out of five patients with anasarca who develop measles there will be a brisk diuresis. Weech[7] has evidence to suggest also that dengue fever may be effective. And in a small group in which we have used modified yellow fever virus experimentally there was evidence that it too could induce a diuresis. Recently a diuresis following infectious hepatitis has been reported.[8] All these infectious agents are viral in nature, and there is no convincing evidence that bacterial or febrile diseases in themselves are effective.

Recently Chasis, Goldring and Baldwin[9] have been administering nitrogen mustard to patients with nephrotic edema. They report that frequently there is a reduction in proteinuria and occasionally loss of

anasarca. The dangers of this drug, however, are so great that for the present it should definitely be considered only as an experimental approach.

We need say little about the mechanical means of removing fluid, such as abdominal paracentesis and the use of Southey tubes. We all resort to these when other approaches fail. In our experience abdominal paracentesis has proven so satisfactory, and redistribution of edema fluid following such a step has been so successful that we do not use the Southey tubes with their attendant discomfort and risk of infection.

The most successful means of reducing edema now is the use of the adrenal active hormones, ACTH and cortisone. Long-term results with these substances cannot be adequately evaluated as they have only been used for two and one-half years, but in that time a certain amount of knowledge has been gained. When a diuresis is induced by either of these hormones it is similar to any spontaneous diuresis in that there is a vast outpouring via the urinary tract of water, sodium and chloride.[10] During the period immediately following such a diuresis the kidneys may be able to handle sodium as a normal kidney does, even at times when the plasma albumin and total protein concentrations are still relatively low. Glomerular filtration rates have been measured by Barnett et al.,[11] and Metcoff et al.,[1] and these in general tend to be somewhat depressed during ACTH administration, but rise during diuresis.

The timing of the diuresis when it occurs is variable. Usually it comes after withdrawal of the medication, but occasionally it happens while the drug is still being given. Before this variability was appreciated two simple alternative explanations of the role played by ACTH or cortisone offered themselves. First, that the induced hyperadrenocorticism might in some way influence the kidney to jettison salt and water. Secondly, the state of hyperadrenocorticism might be followed by a state of reduced adrenal cortical activity when the medication was withdrawn, and this state in turn might be responsible for the diuresis. Were either of these hypotheses correct, then the timing of the diuresis would perforce have to be constant relative to the drug administration, either during or following it. Since the timing is variable, one has to search elsewhere for the explanation. One may hypothesize that these hormones suppress the elaboration of some factor by the pituitary which has been causing the retention of salt and water. Since, however, the materials administered in themselves cause retention of salt and water,

TABLE I.—RESULTS OF HORMONE THERAPY IN THE NEPHROTIC SYNDROME

Preparation Used	*Number of Courses*	*Complete Loss of Edema*		*Partial Loss of Edema*		*No Loss of Edema*	
		No.	*%*	*No.*	*%*	*No.*	*%*
ACTH	62	25	40.3	15	24.2	22	35.5
Cortisone	40	23	57.5	3	7.5	14	35.0
ACTH plus Cortisone	19	11	57.9	3	15.8	5	26.3
All Kinds	121	59	48.8	21	17.4	41	33.8

there would be a conflict between the pituitary suppressive effect and the antidiuretic effect so that usually no diuresis could occur while the hormone is being given. Occasionally, however, it might be that the postulated pituitary suppression would predominate over the exogenous hormone effect and diuresis could begin during treatment.

The ability to induce diuresis in nephrotic patients more or less at will has enabled research workers to characterize quantitatively many of the changes which occur at such a time, but as yet there has been no satisfactory elucidation of the factors which prompt the kidney suddenly to release salt and water. Therefore, let us pass from theoretical considerations to the actual clinical results obtained with these drugs.

There are several reports in the literature showing the effectiveness of adrenocorticotropin in inducing diuresis in nephrosis.[10, 12, 13] Little, however, has been reported with regard to the use of cortisone, and past reports [13, 14] do not suggest that it is as effective as ACTH. Therefore, our experience may be of some interest in this respect.

In the past two and one-half years we have treated 45 patients with either ACTH, cortisone or a combination of the two. We have given more than the 121 such treatments shown in Table I but have included only those which were not interrupted by some complication. In the early days, when our experience with the drugs was limited, a "course" was subject to variation both in duration and daily dose schedule. Since the early work was done almost exclusively with ACTH, this variability of regimen may explain the somewhat smaller percentage of complete successes obtained. Currently, a course for a two to five year old child consists of a ten-day period of administration of the hormones unless

brisk diuresis begins before the end of that time. When ACTH is used it is given in divided doses amounting to 80-100 milligrams daily. With cortisone we give 200 milligrams a day in one intramuscular dose or in divided oral doses. When the combination is used we give ACTH 40 milligrams plus cortisone 50 milligrams daily. Among those treated were three adult patients. When ACTH was used with them it was given at 100 milligrams daily, and with cortisone we gave 250-300 milligrams daily. Two of the three adults responded favorably.

The patients treated, as can be surmised from the earlier remarks, were not selected on the basis of their freedom from signs of "chronic glomerulonephritis," but all types were included provided there was no evidence of severe renal insufficiency. There was no correlation between the effect of treatment and evidence of glomerular disease. Of the forty-five patients, thirty at some time experienced complete delivery of edema in relation to treatment; another eight had at least partial success at some time, and 7 had no significant effect at any time.

Since many of the patients received more than one type of treatment, the results are set down in the table by courses rather than by individual patients. The overall picture shows that complete success—that is delivery of all edema—was achieved about 49 per cent of the time, partial success in another 17 per cent and failure in 34 per cent. Breakdown of the figures into the various types of treatment shows that failures were proportionately about the same with both ACTH and cortisone, and somewhat less with the combination of the two. This latter figure is based on too small a series necessarily to have significance. With the ACTH group there was a smaller proportion of complete successes than with cortisone, a larger fraction having only partial success. This apparent superiority of cortisone may, as we have suggested, be explained on the basis of the smaller ACTH dosage schedule used in the early work. It seems reasonable to conclude that cortisone is at least equally as effective as ACTH. No difference could be detected between the results when cortisone was administered parenterally or by mouth.

Individual patients were very variable in their responses. In Figure 1 are represented the effects of each course on the patients. In this it can be seen that there are, as would be expected, some individuals who showed a favorable response to early courses, but later failed to respond. There are others, however, who showed no response early but did respond favorably later. The last patient represented is a nineteen year

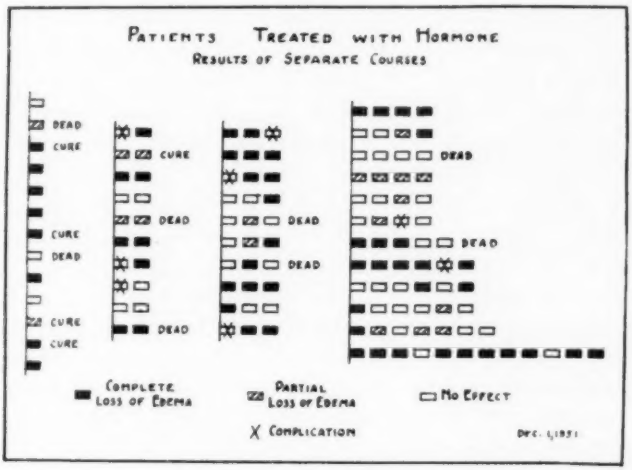

Fig. 1—Chart showing results of individual courses in individual patients. Periods of treatment represented by single rectangles, results indicated by shading. Single cases are represented by the horizontal projection of symbols from the various ordinates. Cases with one course grouped in the first column, those with 2 in the second, 3 in the third and 4 or more in the fourth.

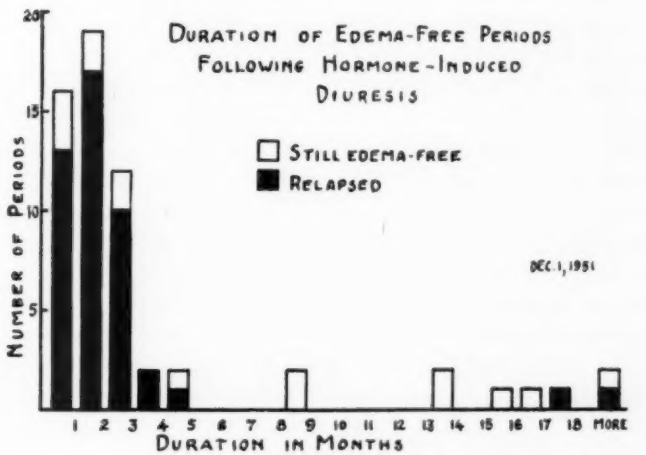

Fig. 2—Showing duration of remissions induced by ACTH, cortisone or a combination of the two.

old boy who has had twelve periods of treatment with ten successes. He has responded equally well to both ACTH and oral cortisone. In this figure one also sees that several patients have progressed to apparent cure (absence of clinical or chemical signs of the disease for a period of at least six months). The fact that these "cures" occurred among those who received only one or two courses suggests that the disease may have been close to the end anyway.

The duration of remission induced by treatment of this type is represented in Figure 2. In this it will be seen that there were many relapses in less than one month, some remissions lasting only a day or two. But there was a large group in which the remission lasted six weeks to three months, and other patients in whom it has been very prolonged.

We have encountered few undesirable effects from these hormones. Since we have been aware that infection may be a real danger while they are being administered, we have lately made it a rule to give full therapeutic dosage of an antibacterial agent during the period of treatment. Occasionally, before this became standard practice, infection did supervene, but in each instance it was easily recognizable and responded to withdrawal of the hormone and appropriate treatment. Also, since renal function may be further suppressed during therapy, we have followed the serum non-protein nitrogen and if there was evidence of deteriorating renal function have stopped treatment. Blood pressure, too, has occasionally risen to levels where we felt it wise to stop. None of these adverse findings has given rise to any serious sequelae.

It is still too early to state with assurance whether there has been any truly beneficial effect on the underlying disease. However, thirteen cases have progressed to either death or apparent cure; of these, eight have died. This proportion is very similar to the experience we have had in the past before treatment when approximately two-thirds died.

In conclusion one may say that the only practical form of treatment which so far has been capable of producing a remission in a high proportion of instances of the nephrotic syndrome is the administration of adrenocortical-active hormones. There is good evidence that cortisone is equally as effective as ACTH. Since cortisone may be given orally and, with certain precautions, safely at home it would appear to be the drug of choice. There is no evidence that it alters the course of the underlying disease but, with our lack of knowledge of how to achieve this, it seems a useful palliative form of treatment.

Summary

The features of the nephrotic syndrome as usually seen in children are compared with the usual picture in adults and the point of view that all such children suffer from a single disease entity is presented. A brief review of some of the forms of attempted therapy is given. Finally, a presentation of our experience with the use of ACTH and cortisone is given. From this it appears that these hormones are the most reliable available agents for inducing remissions and that both agents are equally effective. There is no evidence that they alter the underlying disease process, but they have proven valuable in palliation.

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FETAL AND NEONATAL RISKS RELATED TO CESAREAN SECTION*

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In the past seventy years tremendous strides have been made in the maternal results following cesarean section. Prior to 1882 the maternal mortality was frequently quoted as being 75 per cent or more. Today it has fallen to a small fraction of a per cent. Indeed a recent series[1] of over 2000 consecutive operations has been reported showing a maternal loss of 0.05 per cent, actually slightly less than the death rate following vaginal delivery in the same institution. Lusk,[2] in the first edition of his textbook published in 1882, found it necessary to defend the procedure, which had fallen into such disrepute because of its record of disaster, that it rarely was performed. He pointed out the extremely unfavorable circumstances under which it had been undertaken and felt that the results could be much improved if the procedure was carried out earlier in labor, before rupture of the membranes and not as a last resort in an exhausted and infected patient. He described closure of the classical type of uterine incision with carbolized silk sutures although credit for this surgical innovation is usually given to Sanger[3] who published his report in the same year. In 1887 he performed the second successful cesarean section in New York City in which both mother and child survived, the first having been reported in 1883. In 1888 he reported two more cases so that he must be regarded as the pioneer of the modern operation in this city.

The great change in the maternal outlook has been attained by an appreciation of the relationship of the duration of labor to the development of amniotic sac and uterine infections and that this relationship was accelerated by the presence of ruptured membranes; by improvement in operative technique with the evolution of the lower segment and extraperitoneal operations; by the broad application of antepartum

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care and the adoption of radiological methods for estimating the adaptability of the presenting part to the pelvis; and finally during the past decade by the ready availability of suitable blood for replacement purposes; the use of the sulfonamides and, later the antibiotics to minimize and almost eliminate the serious infectious complications; and the development of improved methods of anesthesia. These latter adjuvants to surgery have resulted in a reduction of maternal hazard estimated to be at least tenfold during this latter period. Today the hazards to the mother following such an operation conducted under proper circumstances can be calculated as being only slightly greater than the mortality following vaginal delivery.

With the increased safety of the operation, it is natural to expect the greater frequency with which it is being utilized at the present time and a broadening of the indications for its performance. In 1882 it was carried out strictly in the interests of the fetus, Lusk[2] stating that it was justifiable only in cases of extreme pelvic contraction, when tumors encroached on the pelvic cavity, and in the presence of extreme carcinomatous degeneration of the cervix. Today we find that the fetal indications are greatly extended with a growing tendency to supplant the more difficult and hazardous type of vaginal operations with cesarean section. In addition it is being used to terminate pregnancies in which serious complications exist, in the interest of the mother rather than the fetus. While this trend is justifiable, one cannot escape the conviction that it is being overdone when series of operations are reported with an incidence above 6-7 per cent. In order to attain a rate higher than this, all forms of vaginal procedures must be abandoned and forgotten except for the use of outlet forceps, an operation which in most circumstances is not strictly necessary. With the abandonment of the more difficult vaginal operations, training, knowledge and skill in their use will be lost. They are not always dangerous to both fetus and mother but only when one fails to estimate all the factors involved in the particular situation in which they are applied. Granted that high forceps operations should be discarded, the mid-forceps operation is still a useful procedure and close to 90 per cent of breech presentations can be delivered with relative safety by the vaginal route. We have continued to use mid-forceps procedures in about 2.5 per cent of our deliveries at Bellevue with the loss, directly attributable to the operation, of two fetuses or newborn infants during the past five years.

We still deliver 90 per cent of our breech presentations by the vaginal route; about once a year we have occasion to regret our judgment on this matter. This conservative attitude, which may not be shared by everyone, may account for the fact that the cesarean section rate on the Bellevue service is at present only slightly over 4 per cent.

With these preliminary remarks dealing with the development of the procedure, demonstrating that the maternal risk constitutes a problem that appears to be well on its way to solution, and commenting on present trends, one may well turn to a consideration of the hazards of the fetus delivered by such an operation. Most reports dealing with cesarean section consider the fetal mortality as only a small facet in the problem as a whole. D'Esopo,[4] reporting on 1000 consecutive operations performed between 1912 and 1947, states that the fetus was lost in thirty-seven instances, a fetal mortality of 3.7 per cent which compared favorably with the gross fetal mortality of 3.3 per cent following vaginal delivery during the same period. In only five instances was he able to relate the loss of the fetus to the operative procedure itself. In four instances the operation was carried out too early in the third trimester; on three occasions because of an error in estimating the duration of pregnancy; once in an effort to secure a live infant for a mother who gave a history of repeated intrauterine death of the fetus. In one instance, the fetus was lost because of vascular collapse in the mother during spinal anesthesia. The remainder he attributes to the maternal complications for which the operation was carried out. Dieckmann,[5] reporting from the Chicago Lying-In Hospital between the years 1942 and 1949, showed a neonatal and stillbirth rate following cesarean section of 5.9 per cent as compared with a rate of 2.4 per cent following vaginal delivery. He emphasizes the role which prematurity plays in the higher rate following cesarean section carried out because of a severe maternal complication appearing well before term, and briefly outlines certain measures that can be followed in an effort to reduce this factor.

More recently reports such as those of Landesman[6] and Huber[7] have appeared which devote themselves purely to the fetal and neonatal hazards of the operation. The former, reporting from the New York Lying-In Hospital, finds that the fetal and neonatal loss associated with cesarean section has decreased between 1933 and 1949 but still remains 2.5 times as great as the over-all rate of the institution. He has analyzed

TABLE I—INDICATIONS

A. Maternal		*B. Fetal*	
Uterine Scar	233	Cephalo-pelvic Disproportion	199
Placenta Previa	58	Breech Presentation	30
Premature Separation of Placenta	14	Other Abnormal Presentations	8
Pre-eclampsia	20	Uterine Inertia	25
Eclampsia	2	Cervical Dystocia	9
Granuloma of Vulva	8	Contraction Ring of Uterus	2
Previous Plastic Operation	7	Premature Separation of Placenta	9
Ruptured Uterus	2	Pelvic Tumor	8
Fibromyomata Uteri	2	Foetal Distress	4
Amniotic Sac Infection with dead fetus	1	Elderly Primiparae	4
		History of Previous Stillbirths	4
		Diabetes	1
		Prolapse of Cord	1
		Postmortem Section	1
	347		303
Miscellaneous	4		
Total	654		

very carefully the factors which underly this difference. In an effort to follow their example, the cesarean sections performed at Bellevue Hospital over a ten year period, 1942 to 1951, have been reviewed with particular emphasis on the fetal and neonatal results.

During this time 654 cesarean sections have been performed. In the earlier part of this period the incidence was about 2 per cent; in the latter it approached or slightly exceeded 4 per cent. Two mothers were lost, one from hemorrhage occurring in a patient with toxemia, and one from cardiac failure. There have been no deaths due to infection. During the ten year period the maternal mortality rate has been 0.3 per cent; over the past five years it has been 0.2 per cent which compares favorably with our over-all rate of about 0.1 per cent. While the indications for these operations were often multiple, it is possible to select the chief indication for which they were performed. These have been listed in Table I dividing them into two groups, dependent upon whether the operation was carried out in the interests of the mother or the fetus. Under the maternal indications are found a large number of secondary operations, the patient usually having had one or more previous cesarean sections, a few of them extensive myomectomies. Since 1948 we have rarely allowed such patients to undergo normal labor. There are found also the various hemorrhagic and

TABLE II

FETAL & NEONATAL DEATHS OPERATIONS PERFORMED FOR MATERNAL INDICATIONS		FETAL & NEONATAL DEATHS OPERATIONS PERFORMED FOR FETAL INDICATIONS	
Uterine Scar	10—4.3%	Cephalo-pelvic Disproportion	7—3.5%
Placenta Previa	10—17.2%	Breech Presentation	1—3.3%
Premature Separation of Placenta	14—100%	Other Abnormal Presentation	1—12.5%
Pre-eclampsia (1 set of twins)	4—20%	Contraction Ring of Uterus	2—100%
Eclampsia	1—50%	Elderly Primipara	1—25%
Granuloma of Vulva	1—12.5%	Fetal Distress	1—25%
Ruptured Uterus	2—100%	Postmortem Operation	1—100%
Amniotic Sac Infection with dead fetus	1—100%		
Diabetes	1—100%		
Recent Fracture of Pelvis	1—100%		
	45		14
FETAL MORTALITY (UNCORRECTED)	13%	FETAL MORTALITY (UNCORRECTED)	4.6%

toxemic complications observed in the last trimester of pregnancy. Finally, there is a group in which, if one excludes the two patients with ruptured uteri, a long range consideration of the patients' interests favored delivery through an abdominal incision. Under the fetal indications cephalo-pelvic disproportion holds high rank, followed by abnormal presentations of the fetus, and abnormalities of the labor mechanism. Contrasting with the complete separations of the placenta classified under the maternal indications and operated upon in the presence of a known stillbirth, are nine instances of partial separation, in all of whom living children were obtained. Finally there is a mixed group in whom delivery through an abdominal incision seemed to favor the chances of the fetus.

As a result of these operations 661 infants were delivered, since among them were found seven pairs of twins. There was a gross fetal mortality of 8.8 per cent, amounting to a loss of fifty-nine including one pair of twins. This is exactly twice our over-all fetal and neonatal mortality which amounts to 4.4 per cent. Correcting both these rates by the elimination of babies or stillbirths weighing under 1500 grams, macerated fetuses, and anomalies incompatible with life, the fetal and

neonatal mortality after cesarean section was found to be 6.3 per cent compared to 3.09 per cent for the service as a whole or still approximately double. Table II shows the fetal and neonatal deaths tabulated in relation to the operative indications. Forty-five of them occurred after cesarean section undertaken in the interest of the mother, a loss of 13 per cent. Only 14 were lost when the operation was performed in the interest of the fetus, a loss of 4.6 per cent. Certain of these categories justify further comment. While the fetal mortality in secondary operations was low, nevertheless the loss of ten fetuses or infants in this group deserves some explanation. Three of these were lost because of prematurity, two because the mother had gone into premature labor, one because of an overestimation of the stage of the pregnancy. One fetus was lost because of a ruptured uterus. In two and possibly more, the type of anesthesia was thought to be a factor. This will be considered later. Seven of the ten fetal or neonatal deaths associated with placenta previa were due to prematurity since circumstances compelled interruption of the pregnancies between twenty-four and thirty-three weeks. One at term was dead before operative intervention was attempted. In one, prolapse of the cord occurred just prior to operation. In the last, maternal shock seemed the likely explanation of the fetal death. The neonatal deaths occurring after operations performed because of pre-eclampsia and eclampsia were due to prematurity; those following rupture of the uterus were due to extrusion of the fetus into the peritoneal cavity and separation of the placenta; the neonatal death in the diabetic was due to hemorrhagic disease of the newborn; the operation in the patient with the recently fractured pelvis was carried out because of the onset of premature labor, the infant dying because of a laceration of the liver and prematurity.

Among the fetal and neonatal deaths, following operations performed for cephalo-pelvic disproportion, were two due to anomalies incompatible with life. Two were due to intracranial injury, in one of which forceps delivery had been attempted. One infant succumbed in the neonatal period to congenital pneumonia. In two, anesthesia appeared to be the important factor. The only fetus lost among the breech presentations showed evidence of embarrassment before the operation was begun. This was also true of a fetus lost in a transverse presentation and of both fetuses in the patients showing contraction rings.

TABLE III—ANESTHESIA

Inhalation Anesthesia		332
approximately one-half cyclopropane-oxygen with or without ether, one half nitrous oxide-oxygen-ether.		
Conduction Anesthesia		
Spinal	285	
Local	35	
		320
Intravenous Anesthesia		2
Resuscitation of the newborn required following:		
(1) inhalation anesthesia		22%
(2) conduction anesthesia		6.8%
(3) intravenous anesthesia		100%

A variety of anesthetic methods were used in these operations, as can be seen in Table III. Almost equal groups were given conduction and inhalation anesthesia, while an intravenous agent was utilized in two instances. Among the patients subjected to inhalation anesthesia approximately one-half were given nitrous oxide, oxygen and ether and one-half cyclopropane, oxygen and ether. Twenty-two per cent of the infants born from operations performed under this type of anesthesia required resuscitation. The proportion requiring resuscitation was slightly greater under cyclopropane, oxygen and ether anesthesia than under nitrous oxide, oxygen and ether, despite the much higher oxygen content of the former. When conduction anesthesia was utilized only 6.8 per cent of the newborn infants required resuscitation. Many patients in both groups had been subjected to labor and to analgesic drugs. However, the difference in the two groups of the reactions of the fetus at birth is striking. Both infants delivered under intravenous anesthesia required resuscitation, an experience which has not encouraged their further use. In addition, there have occurred two long and difficult inductions of anesthesia with nitrous oxide, oxygen and ether in both of which the fetus, apparently normal at the start, was found to be dead at the time of delivery. Another such fatality occurred with deep cyclopropane oxygen anesthesia. Besides these clear-cut instances, the use of inhalation anesthesia may have played a part in at least five other fetal or neonatal deaths. In all of these cases the fetus was already compromised by prolonged labor and showed evidence of embarrassment prior to operation. In all fairness, it must be

stated that three unexplained stillbirths were obtained in operations performed under spinal anesthesia. Nevertheless one must conclude that in this group of cases general anesthesia considerably increases the fetal hazard as compared to the results obtained under conduction anesthesia.

After a consideration of the fetal and neonatal mortality occurring in the material presented, it would appear that discussion might be pursued along four distinct lines. One, the hazards to the fetus related to the stage of pregnancy when the operation was performed;[8] two, hazards due to the operation itself; three, hazards due to anesthesia; and finally, remote hazards in a subsequent pregnancy due to the presence of a scar in the uterus.

1. Pregnancy can be interrupted prematurely by cesarean section under two circumstances, (a) in the presence of a serious complication in the prospective mother such as placenta previa; toxemia of pregnancy; diabetes which has proved difficult to control, or (b) the onset of premature labor in a uterus impaired by an old scar. Interruption at the 28th week of pregnancy offers little chance to the fetus of survival. The closer the patient can be carried to term, the greater chance there is of obtaining a living infant. It has been said recently[9] that the care of premature infants has advanced to such a degree that pregnancy can be interrupted at the 32nd week without serious impairment of the fetal prospects. With this statement disagreement must be voiced strongly since it is believed that at least 15 to 20 per cent will be lost who are delivered between the 32nd and 36th week. It has been shown recently by Wellen[10] that the fetal risk in mild toxemia is not increased by allowing the patient to proceed to term. Only when severe pre-eclampsia develops, which may or may not progress into eclampsia, is the fetal risk greatly increased. Early intervention by cesarean section in this latter group of cases is often necessary in the interest of the mother and in disregard of the fetus. In the former group many infants may be saved and, indeed, abdominal delivery avoided altogether by utilizing induced labor, if the mother is allowed to proceed with the pregnancy, under conservative therapy and under close observation. A similar attitude[11] may often be followed in cases of placenta previa. Cesarean section carried out at the first hemorrhage exhibited by patients with this complication will often be done so early in the third trimester that the premature infant will not survive. The

initial hemorrhage of placenta previa is usually not severe and is almost always self limited. Such patients often can be carried on for several weeks without serious blood loss and can be regarded as being perfectly safe as long as they are under close observation with blood replacement available. Interruption as close to term as possible by cesarean section best serves the interest of both mother and fetus. A similar philosophy[12] may be voiced in regard to the severe and poorly controlled diabetic. Once premature labor has begun in a patient who has previously been subjected to cesarean section, intervention cannot be avoided, providing one does not wish to subject the prospective mother to the immediate and remote hazards that a vaginal delivery will sometimes entail. These remarks have to do with operative intervention in pregnancies known to be premature. Another risk is faced by the fetus in elective cesarean section performed before the onset of labor. Here the operation is performed at a date often set far in advance based on the estimated time of labor. An unexpectedly premature infant may be obtained because of error in calculation. It is well in all such patients to check on the size of the fetus and the character of the maternal soft parts. If the patient does not appear to be at term, operation should be postponed. Finally, in any case subjected to cesarean section in which the fetus is premature, pre-operative medication should be avoided and conduction anesthesia is particularly desirable because of the depressive effects of analgesic and anesthetic agents on the respiratory center of the premature.

2. Hazards to the term fetus or newborn infant because of the operation itself probably are negligible. No longer do we see deep incised[13] wounds of the fetus due to an entry through the abdominal wall and uterus performed in a single slash in order to perform the operation with the utmost speed. The hypothesis, most recently propounded by Bloxsom[14] that the fetus is prepared for respiration by the process of labor, and so begins to breathe more readily after normal vaginal delivery than after delivery through an abdominal incision, is no longer tenable. Considerable light has been thrown on the respiratory mechanism of the fetus during the past fifteen years. The existence of respiratory movements in the fetus, first suspected by Ahlfeld[15] has been proved definitely by the experiments on rabbits by Snyder and Rosenfeld[16] and verified in the human by Davis and Potter.[17] Extrauterine respiration, therefore, is but a continuance of the function already in ex-

istence in utero, its different character being in all likelihood due to the change of the media which is being respired. The lung, of course, takes on a much greater functional importance since it takes over the burden of gaseous exchange from the placenta. It has been demonstrated[18] that the fetal blood before the onset of labor is relatively unsaturated with oxygen and even less so after vaginal delivery.[17] In fact the experiments of Snyder and Geiling[19] on rabbits during parturition suggest that the greatly increased proportion of stillbirths obtained after the administration of morphine are due, not to the drug but to the prolongation of labor. The adverse effects of prolonged labor on the human fetus have recently been studied by Corner and his associates[20] who find, in a series of such cases subjected to rigid criteria, that there was a fetal mortality of 18 per cent, 79 per cent of which were due to asphyxia. It seems safe to say that the term infant suffers no greater hazard from abdominal delivery itself than from a short normal labor and certainly less risk than when it is subjected to a protracted labor.

3. Anesthesia in the patient subjected to cesarean section presents a problem quite different from that encountered in the average run of surgical procedures. In addition to the patient herself one must consider the fetus. The respiratory center of the latter, as has been shown experimentally by Rosenfeld and Snyder,[21] and by innumerable reports on clinical human material, is especially vulnerable to analgesic and anesthetic drugs which readily pass the placental barrier. In regard to the barbiturates,[22] there is evidence that they accumulate in the fetus in higher quantities than they do in the mother, indicating that the fetus may be deficient in its capacity to destroy them. All gaseous and volatile anesthetic agents have been shown to depress the fetal respiratory center even when given in a dosage which has no observable effect upon the mother. Slight degrees of anoxemia in the mother, if maintained for thirty or forty minutes, may have a lethal effect on the fetus, already existing under a state of low oxygen tension prior to the onset of labor. Such effects may be produced more frequently and more rapidly if the fetus has been subjected to prolonged labor with ruptured membranes,[19, 20] which from clinical and experimental results would seem to favor the development of an anoxemic state. Nitrous oxide[21] has been demonstrated as being dangerous to the fetus if it is given for any length of time with less than 20 per cent

oxygen. Cyclopropane anesthesia,[23] even with its high proportion of oxygen, results in the delivery of a high percentage of partially asphyxiated babies. This may be related to the strong tonic contraction of the uterus, frequently observed under this anesthesia, which may well interfere with the circulation of maternal blood in the placental sinuses and, therefore, with the gaseous exchange between it and the fetal blood. If carried to the lower planes of stage three before the delivery of the fetus it may result in irreversible fetal respiratory depression. Our fetal results from inhalation anesthesia might well be worse were it not for two factors peculiar to the fetus; one,[24] the absence of a carotid body reflex and, two,[25] a marked resistance to the effects of profound anoxemia. The absence of the former prevents the stimulation of deep respiration by low oxygen tensions and a resultant flooding of the lungs with excessive amounts of amniotic fluid. The presence of the latter prevents the dire effects of deep asphyxia which occur in a few minutes in the adult organism. The former appears within a few weeks after birth; during the same period the capacity for resisting anoxemia rapidly disappears in the infant. If inhalation anesthesia is to be utilized for cesarean section it should not be carried below plane one of stage three and a sine qua non is rapid delivery of the fetus at the earliest possible moment after the anesthesia is commenced.

From the above remarks, it can be readily seen that conduction anesthesia possesses special advantages in the performance of cesarean section since it can in no way directly affect the fetus in utero. The common forms of conduction anesthesia utilized for this operation are local, highly recommended by Beck[26] and, more recently, by Landesman,[6] and spinal anesthesia endorsed by Eastman,[27] Acker et al.[28] and others.[1, 29] Local anesthesia, providing an adequate technique is carried out, is almost absolutely safe as far as the mother is concerned but has the disadvantage that it is a slow and tedious procedure. The limitations of this form of anesthesia consist of those situations which demand a rapid delivery of the fetus and the emotional make-up of the prospective mother. Spinal anesthesia, although involving greater hazards to the mother, is becoming more and more popular. It can be administered quickly and with safety to the mother providing that the position of the patient is kept in mind, and that the blood pressure is observed constantly. Any tendency to hypotension, which may have

disastrous effects on the fetus, can be effectively counteracted by the use of vasopressor drugs such as ephedrine or neosynephrine. However, spinal anesthesia has definite limitations. It carries added risks when utilized in patients with a history of neurological disease or evidence of syphilis; in patients with severe hypertension or hypotension; in those exhibiting very severe degrees of anemia; or when any infectious condition is present on the skin of the back. As in the case of local anesthesia, emotional antagonism on the part of the patient may prevent its use.

In neither of these forms of conduction anesthesia is it necessary to obtain long periods of action since inhalation anesthesia may be safely superimposed once the fetus is delivered. Before this has been accomplished, certain observers[28] believe that the administration of oxygen to the mother may be helpful to the fetus. All that has been said previously becomes of special importance when the fetus about to be delivered is premature.

Conduction anesthesia, in some form, would appear to be much more favorable to the fetus than inhalation anesthesia. It can be used safely in the large majority of instances and is highly regarded on the Bellevue service, though the figures presented on our tables do not convey this impression. Inhalation anesthesia should be reserved for a small group of patients, presenting special indications, and given with care, skill and understanding. It is a little difficult to understand the remark of Dieckmann[5] who has utilized spinal anesthesia at the Chicago Lying-In Hospital very successfully, that he would prefer nitrous oxide, oxygen and ether if competent anesthetists were available. It would seem even more important to have a competent anesthetist available for spinal anesthesia, which while safe for the fetus, may present greater risks to the mother.

4. Once a patient has been subjected to cesarean section she presents a special risk to the fetus in any subsequent pregnancy—that of rupture of the uterus. This accident often entails the loss of the fetus, may result in uterine injury sufficient to require removal of the uterus and sometimes results in a maternal death. Its possibility should be the main reason for combating the unrestricted widening and relaxation of the indications for performance of the operation. Parenthetically it can be stated that an unrestricted cesarean rate[1] will undoubtedly result in a greatly lowered fetal mortality after the cesarean section since many

more babies will be delivered by this method who also could have been safely delivered by the vaginal route. A somewhat extreme instance can be quoted of a young woman who had an adequate pelvis who was delivered by cesarean section after a few hours of labor because she had a breech presentation. The infant proved to have an incapacitating congenital anomaly of the heart and was given a poor prognosis. In her next pregnancy she ruptured her uterus at the eighth month resulting in a stillbirth and such extensive uterine injury that hysterectomy was necessary. Brierton,[30] in recent study of the material at five New York hospitals found that about 3 per cent of such patients will rupture their scars, some before the onset, but the majority after the onset of labor. This accident is twice as common with classical scars as compared with those in the lower segment of the uterus. The fetal and neonatal mortality was 46 per cent, the maternal mortality 3.8 per cent. Since the maternal risks of cesarean section have been reduced so strikingly of late years, it is believed that all patients, once subjected to cesarean, should be delivered in subsequent pregnancies by such operation. Such a policy should reduce both the maternal and fetal hazards which the presence of a uterine scar entails. So far as the fetus is concerned, an occasional operation will have to be performed because of the onset of premature labor; since these operations are commonly performed electively, an occasional premature fetus will be delivered unexpectedly unless extreme care is used; and finally all risk cannot be removed since in a minority of instances rupture takes place unexpectedly before the onset of labor. This policy is becoming more and more common. It was adopted on the Bellevue service following the occurrence of the tragic case outlined previously. Since that time 176 secondary operations have been performed with the discovery of seven ruptures of the uterus, four of them incomplete, a peritoneal window being present; an incidence of 4 per cent. No fetal deaths have occurred as a result of rupture and no uteri were sacrificed. All the mothers recovered uneventfully. During this period an occasional patient in this category was delivered vaginally because of the lateness of her arrival at the hospital. In a hospital[31] where this policy is not being followed, two such cases have been reported recently; the patients, upon being allowed to go into labor, ruptured their uteri, resulting in the loss of one fetus. Furthermore, the injury was so extensive that hysterectomies were necessary in both cases. The patients recovered uneventfully.

Conclusions

I. Fetal and neonatal mortality associated with cesarean section will remain higher than that associated with vaginal delivery providing strict indications are followed for the performance of the operation.

II. Fetal and neonatal mortality can be (a) diluted or artificially reduced by an unrestrained use of the operation, or (b) actually reduced by

(1) carrying the prospective mother as close to term as is compatible with her safety;

(2) by adequate and efficient care of the premature infants born of many of these patients;

(3) the avoidance of excessively long trial labors, and over-vigorous attempts at instrumental delivery in the presence of obvious obstacles;

(4) the intelligent use of anesthesia with proper regard to the fetus, particularly when premature or already showing evidence of embarrassment;

(5) the availability in the operating room of adequate instruments for resuscitation and individuals adept in their use;

(6) the diminution of the hazards entailed by the presence of a uterine scar by

(a) the avoidance of unnecessary primary operations;

(b) by delivering cases subjected to cesarean by a similar operation, preferably elective, in subsequent pregnancies.

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SPINAL CORD AND LOCAL SIGNS SECONDARY TO OCCULT SACRAL MENINGOCELES IN ADULTS*

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ATYPICAL and apparently paradoxical symptoms and signs of spinal cord disease may accompany occult sacral meningoceles in adults, so that local signs of sacral nerve root involvement, such as bladder and rectal dysfunction or pain and disability in the low back and lower extremities, may be masked and thus lead to errors in diagnosis.

The fact that gross neurological symptoms of a sacral meningocele may not appear until the second or third decade of life, together with the fact that sacral meningoceles are relatively rare and hence seldom considered, may add to the difficulties of diagnosis. However, when spinal cord signs accompany a sacral meningocele they are usually progressive without remissions and are generally confined to the lower cord segments, thus tending to rule out the diagnosis of multiple sclerosis and other diffuse degenerative diseases of the spinal cord.

The rarity of the condition is indicated by Ingraham[1] in his comprehensive bibliography and monograph covering the last two centuries. He states that while nearly 25 per cent of normal children have some form of occult congenital vertebral defect, of sixty-five low spinal meningoceles at the Children's Hospital of Boston, only one was confined to the sacral canal.

The diagnosis of these lesions is of course greatly aided by x-ray studies, plain and myelographic, and frequently by the presence of associated congenital defects such as a telltale lipoma,[1-4] a dermal or pilonidal sinus,[5] maldevelopment of an extremity or the urogenital tract,[2] etc.

While the surgical treatment of a spinal meningocele was first reported about 100 years ago,[1] surgery has been carried out with effec-

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tiveness only during the last fifty years or so, and more especially in the past twenty-five years. As late as 1920 indeed, treatment was often restricted to aspiration or sclerosing injections of the sac.

Report of Two Cases with Spinal Cord Involvement

Case 1. This 40 year old female was admitted to the Neurological Institute of New York, Presbyterian Hospital, on June 3, 1951. There was no family history of congenital malformations and her two daughters developed normally.

The patient first noted symptoms of slowly progressive pain and paresthesias in the left hip and anterior as well as posterior aspect of the left thigh at the age of 22, following her first childbirth. She stated however that the left leg had always been shorter and thinner than the right, presumably due to "infantile paralysis."

At the age of 30 a progressive tendency to urinary frequency began, followed soon thereafter by incontinence on straining. More recently she began to suffer increasing but poorly localized aching pains, paresthesias and weakness of the left leg after standing for ten minutes.

Eight years before admission she was told that surgery would be of no avail and a spinal brace was prescribed which she wore faithfully but without benefit for the ensuing eight years.

Six years ago in 1945 an extensive abdominal operation for fixation of the urinary bladder and the uterus failed to relieve her symptoms. The past history was otherwise non-contributory.

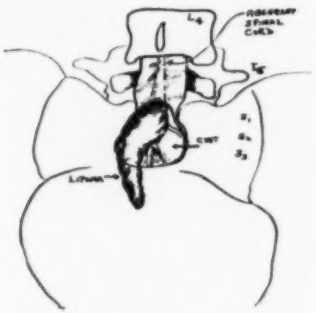
On neurological examination there was a marked limp of the left leg which was ¾ inch shorter than the right. Its muscles were diffusely atrophic, weak, and subject to spontaneous fibrillations. Hyporeflexia of the left patellar and hamstring reflexes, absence of the left suprapatellar and Achilles reflexes, and a positive left Babinski sign were demonstrable. Occasional involuntary "spasms" or contractions of the left hamstring muscles were observed. There was reduction of touch, pain and temperature perception over both the anterior as well as the posterior aspects of the left thigh and the lateral aspects of the left calf. The neurological examination was otherwise within normal limits, and no spinal or sacral tenderness, masses or defects were noted.

Routine laboratory tests were within normal limits except for x-ray evidence of marked widening of the sacral canal extending into the arch and body of the sacrum, and a small sacral spina bifida.

Fig. 1. Myelogram (6 cc. Pantopaque) showing site of sacral meningocele (lowermost collection of dye).

The sacrum and coccyx were curved to the right of the midline suggesting a so-called "scimitar" sacrum.[2, 3] Myelography with 6 cc. pantopaque revealed a large meningocele in the body of the sacrum with a small lateral extension to the left of S-1 (Figure 1). The thoracolumbar canal appeared normal, and the cerebrospinal fluid (CSF) findings were entirely normal.

Surgical exploration of the sacral lesion was elected in view of the rapidly progressive and disabling pain, paresthesias, and weakness of the left leg together with bladder dysfunction. It was difficult however to account for all the neurological findings on the basis of the sacral lesion alone, for their character and distribution not only indicated involvement of nerve roots at a higher level but also showed clear evidence of spinal cord involvement. The paradoxical nature of these signs was further suggested by the fact that the pain and paresthesias did not follow any recognized dermatomal or nerve root distribution. However,



Occult Sacral Meningocele

Fig. 2. Case 1, showing lipoma, cyst, and abnormal extension of spinal cord into sacral canal.

the operative findings explained the clinical picture at once.

Operation: June 8, 1951. Under general anesthesia the sacrum was unroofed through a midline incision, disclosing a large fusiform lipoma which immediately bulged into the wound (Figure 2). The lipoma blended inextricably with the dura along the left side of the sacral canal. On opening the dura above and to the right of the lipoma, a large cystic cavity was found, lined with arachnoid and filled with clear CSF, occupying the bony cavity of the sacrum from S-1 to S-4. At its upper end the cyst was continuous with somewhat dilated lumbar subarachnoid space.

Extending down through the entire length of the lumbar canal and sacral meningocele was a small but well-formed spinal cord about 7 mm. in diameter. Asymmetrical dorsal and ventral nerve roots emanated from both sides of its dentate ligaments at various angles.

As it was impossible to remove the lipoma without injury to contiguous nerve roots, the dura and overlying structures were closed in layers, with the hope and expectation that the bony decompression would relieve local compression and remote traction effects upon the abnormal spinal cord and its nerve roots.

Course: Aside from inability to void for ten days after operation, requiring tidal drainage, the patient made an uneventful recovery. Dur-

ing the six months since operation she has not only enjoyed satisfactory bladder control, but increased power and markedly reduced discomfort in the left leg. Her brace has been discarded and both she and her family are well pleased at her postoperative gains.

Comment: The paradoxical neurological signs indicating spinal cord involvement were undoubtedly due to the fact that the spinal cord in this case extended all the way down to the lower end of the sacral canal where traction or pressure upon the cord and its nerve roots by the large lipoma as it grew must have induced her progressive neurological symptoms and signs. It is also possible that the lipoma had so anchored the aberrant spinal cord that normal bodily movements tended to stretch it and thus produced changes leading to progressive spinal cord degeneration and nerve root irritation. Walker[4] describes a case duplicating this one in all respects and also mentions these possibilities in explanation of the onset and progression of symptoms and signs so late in life. He too reported improvement following surgery, as have others.[2-8]

Case 2. This 30 year old male, admitted to the Neurological Institute of New York, Presbyterian Hospital on February 5th, 1951, was healthy and well until 1945 when he first developed right "sciatica" after extensive and rough jeep driving in the U. S. Army overseas. In April of 1950 he suffered sudden severe low back pain on lifting heavy bags and shortly thereafter noted a mid-abdominal girdle distribution of disagreeable itching sensations. A month later progressive constipation and weakness of both legs began, plus occasional urinary incontinence and decreased libido. Neurological examination at another clinic in June of 1950 disclosed unsteadiness of gait, hyperreflexia of the left lower extremity with ankle clonus and a positive sign of Babinski, absence of lower abdominal reflexes, and a vague sensory level at T-6. The cranial nerves and remainder of the neurological examination were reported as normal. A myelogram was said to have been normal, and the CSF total protein 51 mg. per cent. During the next 6 months all the above symptoms and signs progressed to an alarming degree, both legs now being affected. A second myelogram was then done at the same clinic and again said to have been negative. The CSF total protein was now 59 mg. per cent. A diagnosis of multiple sclerosis or vitamin B deficiency was entertained and he was discharged with a prescription for massive doses of vitamin B_1 and B_{12}.

On February 5, 1951, when admitted to the Neurological Institute of New York, the patient had an advanced spastic slapping type of gait, bilateral hyperreflexia and positive Babinski signs in both lower extremities together with marked weakness, spontaneous clonus and pronounced impairment of all forms of sensation save position up to the level of T-8. Hyperpathia of the antero-lateral aspects of each thigh and saddle area was also noted. No abnormal symptoms or signs referable to the cranial nerves or upper extremities were elicited but the patient complained of marked bladder and rectal dysfunction, sexual impotence, and constant burning pain in both thighs.

Laboratory Data: The hemogram, blood Mazzini test, erythrocytic sedimentation rate, hematocrit, urinalysis and gastric analysis were all within normal limits.

X-rays: Review of the films taken elsewhere were normal as to skull, chest and dorso-lumbar spine. Myelogram films revealed no abnormalities in the cervical, thoracic or lumbar region, but showed a sizeable meningocele in the sacral portion of the spinal canal.

Lumbar puncture revealed slightly xanthochromic CSF with normal pressure and dynamics, a total protein of 90 mg. per cent and 18 WBC per cu. mm. The colloidal gold curve and Kolmer tests were negative.

Recommendation: It seemed clear that there must be two presumably related pathological processes: one, the occult sacral meningocele with local (sacral) root involvement; the other, a spinal cord lesion extending as high as T-6, possibly a syrinx. Some examiners felt that arachnoiditis, varicosities, or some obscure degenerative disease or possibly multiple sclerosis affected the spinal cord. They did not recommend surgical intervention. Since it was clear, however, that the patient was doomed unless he could be helped by surgery, operation was agreed upon with the intention of exploring both the spinal cord and the sacral lesion at the same time.

Operation: February 26, 1951. Under general anesthesia the two intraspinal operative exposures were carried out: (a) laminectomy from T-6 to T-9 inclusive and then (b) exposure of the sacral meningocele. The latter proved to be a large sac filled with clear fluid and lined with arachnoid, occupying the enlarged upper three segments of the sacral canal. Nerve roots were incorporated in the walls of this sac. At the upper pole a narrow neck about 2 mm. in diameter formed the only communication with the subarachnoid space of the lumbar canal.

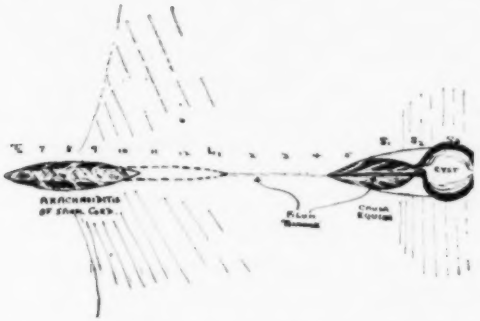


Fig. 3. Case 2, showing relation of filum terminale to sacral meningocele. Traction on both these structures induced spinal cord motion.

No dermal sinus, lipoma or aberrant spinal cord was apparent. However, the filum terminale was seen to merge with and thus be attached to the dura forming the upper or cephalic aspect of the meningocele.

The spinal cord within the depths of the upper exposure looked moderately atrophic and was surrounded with thickened, densely trabeculated arachnoid. There was no evidence of a tumor or syrinx. It was concluded that the findings indicated spinal cord degeneration and secondary arachnoidal adhesions.

The significant feature of the operation was the fact that the filum terminale was so taut that the least traction upon it at the lumbosacral region resulted in a visible stretching effect upon the spinal cord at the mid-thoracic level. Traction on the wall of the meningocele close to the attachment of the filum terminale also tended to stretch the spinal cord (Figure 3). It seemed quite likely, therefore, that the jolting trauma of rough jeep riding and subsequent heavy lifting must have been transmitted through the meningocele and taut filum terminale to the spinal cord, where mechanical stretching and tugging effects eventually produced degenerative spinal cord changes. In other words, the sacral cyst acted like a bag of water hung on the end of the spinal cord by a tight string.

To alleviate this stretching effect the filum terminale was divided between silver clips at the lumbo-sacral level. An opening for free fluid communication was then made between the lumbar subarachnoid

space and the interior of the meningocele sac and the operative wounds closed in the usual fashion.

Course: Aside from a temporary increase of bladder dysfunction the patient made an uneventful postoperative recovery. During the past year he has shown steady and pronounced improvement in gait, motor power, reduction in "spasticity," disappearance of burning pain, and improved bladder and bowel function. He also regained sexual ability. In a word, he is gratified not only by the arrest of his former downhill course but also by the positive gains just enumerated. Whereas it had become impossible before operation to drive his car, he can now do so without difficulty.

Comment: This case indicates how and why an occult sacral meningocele may be associated with remote spinal cord changes that may simulate a primary degenerative disease of the spinal cord that may be interpreted as multiple sclerosis.

In cases having evidence of atypical degenerative disease of the thoraco-lumbar portion of the spinal cord, therefore, an occult sacral meningocele should be considered.

Parenthetically another point of practical diagnostic importance is the fact that postural headaches may sometimes be caused by occult meningoceles at the lower end of the spine, presumably because of sudden alterations of cerebrospinal fluid pressure caused by changes in posture or local pressure over the cyst.

Summary

1. Two cases of occult sacral meningoceles in adults are described.

2. Spinal cord signs were apparent in both cases. In Case 1 an abnormally long spinal cord extended down through the sacral meningocele where it was subjected to direct compression by an associated lipoma. In Case 2 spastic paraparesis and sensory signs as high as T-8 reflected indirect spinal cord changes apparently due to trauma transmitted to the spinal cord from the remote sacral meningocele by the filum terminale.

3. Local signs of sacral nerve root involvement in each case included pain in one or both legs and bladder dysfunction.

4. Headaches on postural change (though not present in these two cases) may be caused by occult sacral or lumbosacral meningoceles in adults.

5. Trauma initiated the overt onset of symptoms and signs in both cases (childbirth in one; jeep riding and heavy lifting in the other).

6. Marked improvement in each case followed surgery which resulted in decompression of the sacral lesions, and release of the spinal cord, respectively, from local compressive and remote traction effects.

7. Serious delay in operative intervention was due in both cases to initial errors in diagnosis as well as unwillingness to recommend surgery.

Conclusions

1. Occult sacral meningoceles may induce spinal cord changes that may simulate other neurological syndromes such as multiple sclerosis and late effects of poliomyelitis. Therefore, x-ray studies of the sacral canal should be considered in bizarre cases of these types.

2. Surgical intervention should be carried out promptly in cases of occult sacral meningoceles in adults before irreversible nerve root and spinal cord changes occur.

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ON THE METABOLIC DEFECT IN GOUT*

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AMONG the arthritides, gout is characterized by an error in the metabolism of uric acid which results in an elevation of the level of serum uric acid and a tendency toward the precipitation of salts of uric acid, urates, as tophi in the cartilages. Whereas the relationship between the acute recurrent inflammatory lesion in the joints and the metabolic defect in the handling of uric acid by the gouty subject is today obscure, this defect in metabolism is in itself of sufficient interest to warrant study. It has been the purpose of the present investigation to explore this abnormality with the aid of currently available research methods.

Clinical collaboration has been an essential feature of this program, since gout is a disease peculiar to man, and this has been supplied initially by Dr. Forsham of the Peter Bent Brigham Hospital, Boston, and, more recently, by Dr. Gutman and his collaborators, Drs. Yü and Bien at Goldwater Memorial and Mt. Sinai Hospitals, New York. In our laboratory, Mrs. Benedict and Dr. Roche have assumed the major share of the responsibility for the work.

Our first studies related to the distribution of intravenously injected isotopically labeled uric acid in normal man.[1] Uric acid was so synthesized as to contain nitrogen enriched with N^{15}. Normal men were maintained on essentially purine-free diets sufficiently rich in protein to preserve nitrogen balance. Each subject received a single small intravenous injection of isotopic uric acid and thereafter uric acid was isolated in pure state from daily urine samples and analyzed on the mass spectrometer for abundance of N^{15}.

Essentially two types of information can be obtained from such an experiment. The "miscible pool of uric acid" is defined as that quantity of uric acid in the body of the subject which is capable of mixing promptly with intravenously injected uric acid and consequently of

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diluting its isotope. From a comparison of the concentrations of N^{15} in the uric acid injected and in that present in the body at the moment of mixing, together with knowledge of the quantity of uric acid injected, the quantity of uric acid present in the miscible pool may readily be calculated. The second type of information relates to the fact that with the passage of time after the initiation of such an experiment, the concentration of N^{15} in the uric acid of the body declines. This fall is a consequence of the continuous generation of new, nonisotopic uric acid molecules by the operation of normal body processes, and the mixing of this newly formed uric acid with the now labeled uric acid in the miscible pool. From the rate of decline in N^{15} abundance, the rate of generation of uric acid, or its turnover, may be estimated.

In four normal subjects studied by this technique,[2] the miscible pool contained an average of 1131 mg. of uric acid with values ranging from 866 to 1341 mg. From estimates of plasma volume and determinations of serum uric acid concentration, it could be calculated that very nearly 1/6 of the uric acid contained in the miscible pool was dissolved in plasma water, whence it was concluded that 5/6 was in solution in extra-vascular water (Fig. 1, N). If it is assumed that all of the uric acid in the miscible pool is uniformly distributed throughout all of the body water, a mean concentration may be computed equalling about half that actually determined in the serum. From this it follows that uric acid is not uniformly distributed, that in fact there are portions of the body water far poorer in uric acid than is the plasma.

From the rate of decline in abundance of N^{15} in urinary uric acid, it could be shown that from 50 to 75 per cent of the uric acid contained in the miscible pool was normally replaced each day by newly formed, nonisotopic uric acid.[1] This requires that each day a quantity of from 500 to 850 mg. of uric acid be introduced into the miscible pool, presumably arising largely from the oxidation of purines contained in nucleic acids and nucleotides of the body. It was of interest to compare these values with the corresponding quantities of uric acid excreted daily in the urines of these normal subjects. Such a comparison revealed that in each case the quantity of uric acid entering the pool exceeded the quantity leaving the pool by the urinary route by a matter of 100 to 250 mg. of uric acid per day. In view of the fact that in normal man on a purine-free diet there was no reason to suppose that the size of the miscible pool of uric acid is increasing, the conclusion appeared inevi-

table that uric acid was leaving the pool by routes other than urinary excretion. We have not explored all possible routes, such as loss in feces and sweat. One route which we have explored is that of catabolic breakdown. In several experiments we have found low but significant concentrations of N^{15} in the urinary urea and ammonia excreted by subjects who had received N^{15} exclusively in the form of intravenous uric acid, proving that to a limited extent catabolism of uric acid does proceed in man. Considered together with the observation of a far more extensive catabolic breakdown of uric acid occurring in man following its oral rather than intravenous administration,[3] it appears likely that the site of this catabolism is in the lumen of the gastrointestinal tract.

When isotopic uric acid was administered to patients suffering from gout, a consistent finding was that the miscible pool of uric acid was greatly increased in size. Thus in a mildly diseased man, whose past history revealed two attacks of acute gouty arthritis, who exhibited no overt tophi, whose serum uric acid was but little elevated (6.9 mg. per cent) and who had no symptoms at the time of the experiment, the miscible pool of uric acid was found to contain 4742 mg. or about four times the normal value. Similar values have been obtained in other patients both by us and by Bishop *et al.*[4] We were fortunate in securing the cooperation of a very severely affected subject, a sixty-four year old man with a twenty-five year history of gout with repeated attacks of acute arthritis and extensive tophaceous involvement of fingers, elbows, knees and toes. This subject has been studied on three separate occasions by the procedure of intravenous injection of isotopic uric acid.[2] On the first occasion he was found to have a miscible pool of 18,450 mg. of uric acid or about 15 times the normal value (Fig. 1, A). Some months later, after a period during which no medication was regularly taken and diet was uncontrolled, he was again examined and found to have a miscible pool of uric acid of some 31,000 mg. or about twenty-five times the normal value (Fig. 1, B). The patient was then placed on a regimen of acetylsalicylic acid (2.4 to 3.6 gm. daily) which resulted in a uricosuria amounting to some 300 mg. of uric acid per day above his basal level. After four months he was again seen and studied. It was found that his miscible pool had contracted to 2084 mg., about 1/15 of the previous value and only about twice the level seen in normal subjects (Fig. 1, C). It should be pointed out that essentially no change in the level of uric acid in the serum (9.8 ± 0.4 mg. per cent) accom-

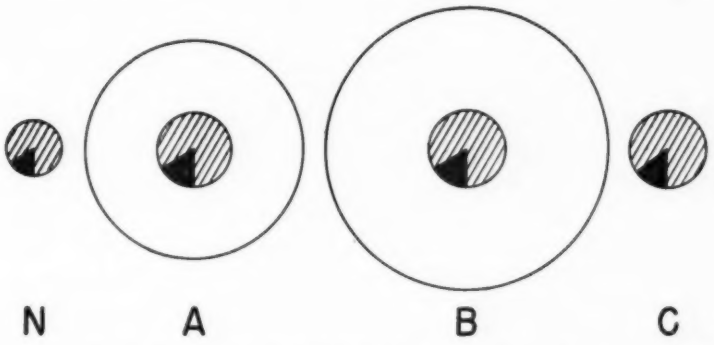

Fig. 1. The Miscible Pool of Uric Acid and Its Compartments.

The areas enclosed in the outer circles are proportional to the milligrams of uric acid contained in the miscible pools in the average of four normal subjects (N), and in a gouty subject on three successive occasions (A, B and C). The black area represents uric acid dissolved in plasma water, the shaded area represents uric acid in solution in extravascular water, the unshaded area (A and B) represents miscible uric acid derived from the urates of the tophi. Between experiments B and C, the patient received acetylsalicylic acid in uricosuric doses.

panied these wide excursions in the quantity of uric acid in the miscible pool.

The magnitude of the miscible pool of uric acid in this subject prior to uricosuric therapy was far greater than could be assumed to exist *in solution* in the body water, in view of the known relative insolubility of uric acid in water at physiological pH and temperature. We were therefore forced to the conclusion that in the gouty subject the superficial layers of the urate masses situated as tophi in the cartilages contributed to the miscible pool of uric acid. If the assumption is made that the distribution of uric acid *in solution* between plasma water and non-plasma water was the same in the gouty as in the normal man, the quantity of uric acid which was included simultaneously in the miscible pool and in the urate of the *solid phase* could be calculated. The results of these calculations are presented graphically in Fig. 1. Here it will be seen that while in the normal subjects all of the uric acid in the miscible pool is in solution, in our severely gouty subject, the largest compartment of the miscible pool of uric acid is in the solid phase (A and B). After the completion of a successful course of salicylate therapy (C), the miscible pool contracted and this contracture was entirely due

to disappearance of that component which had initially been in the solid phase.

The finding that urate in the solid phase contributes to the miscible pool implies that a continuous solution and precipitation of urate is occurring at the interface between tophus and body fluid. This is not dissimilar to the equilibration between the liquid and solid phases believed to be taking place with respect to the inorganic constituents of bone salts.[5] Support of this view was found in the study of a tophus excised in the course of one of the isotope experiments in which it was determined that whereas little or no isotope could be demonstrated in the centrally located urate, the peripheral layers of urate yield uric acid enriched with N^{15}.

It must not be supposed that any startling decrease in the clinically estimated mass of tophi was observed in the patient during the period of salicylate therapy. As a matter of fact, no decrease in size was noted but this is not surprising in view of the fact that whereas some 29 gm. of uric acid had been mobilized from the solid phase, this clearly represented only a very small fraction of the urate present in tophi in this subject. It was considered of interest to have established the fact that some degree of equilibration did exist between uric acid in the body fluids and urates in the tophi since this indicated that the deposition of urate in tophi was at least to some extent a reversible process. Not all of the urate was in such an equilibrium relationship and obviously the dry central portions of larger tophi, no longer in contact with body water, are excluded from such an equilibrium.

The effect of adrenocorticotropic hormone upon the quantities under consideration has also been studied. This agent was known to produce an increase in the quantity of urinary uric acid and it had been suggested that an accelerated breakdown of nuclear material contributed to the increase. Both in normal and in gouty subjects we have studied this effect of ACTH and in every case, the increase in urinary uric acid was accompanied by a fall in the level of serum uric acid. A coincident increase in rate of fall of the N^{15} concentration in uric acid, which would have been anticipated in the event of increase in rate of endogenous uric acid production, could not be detected, and we have therefore concluded, in harmony with others,[6] that the uricosuric effect of ACTH is not at the level of uric acid production but rather at the level of renal excretion of uric acid. Insofar as uric acid is concerned, the effect of

ACTH appears to be one of interference with reabsorption by the renal tubule.

These studies with isotopic uric acid have been useful in that they revealed the large increase in the quantity of miscible uric acid which is present in the body of the gouty individual. They failed however to give a clear indication of the nature of the disturbance which led to this increase. As with many other body constituents, the uric acid in normal man is in a "dynamic steady state"[7] by which is meant that its quantity remains sensibly constant, not because it is inert, but rather because its rate of elimination and destruction is precisely matched by its rate of generation. When, under pathological circumstances, the quantity of uric acid increases, two possible mechanisms must be considered as contributing to such an increase. On the one hand, the rate of elimination may be reduced, on the other hand, the rate of generation may be enhanced. Often it has been possible to gain insight into the rate of generation of a body constituent by observing the rate at which isotope appears in that product when an isotopically labeled precursor is administered. Since glycine has been shown to be a specific precursor of atoms 4, 5 and 7 of the purine nucleus,[8, 9] it was determined to conduct experiments upon normal and gouty human subjects, following the abundance of N^{15} in urinary uric acid after the administration of isotopic (N^{15}) glycine.

The major difference in procedure in these experiments, as compared with those in which uric acid was the test substance administered, was that in the present series the glycine was administered *by mouth* well mixed with the protein of the diet. The reason for the selection of the oral route of administration was the fact that individual amino acids are known to be better tolerated if administered together with a complete supplement of amino acids, that the optimal utilization of any amino acid for protein synthesis requires the simultaneous availability of all the other necessary building stones of body protein.[10]

When an amino acid labeled with N^{15} in the α-amino group is administered to a normal mammal, the isotopic nitrogen distributes itself widely not only by distribution of the labeled amino acid but also by a host of reactions which transfer α-amino nitrogen from the amino acid to other compounds. In man, classified as a *ureotelic* animal in that he eliminates nitrogen chiefly in the form of urea,[11] much of the isotopic nitrogen fed as an amino acid will appear fairly promptly in urinary

urea. In our experience in the neighborhood of 20 per cent of the N^{15} fed as glycine is excreted as urea within twenty-four hours, and up to 50 per cent appears as urinary urea in ten days.

By way of contrast it may be pointed out that not all species are capable of generating urea. The bulk of the urinary nitrogen excreted by birds is in the form of uric acid and such animals are said to be *uricotelic*. In birds the administration of indifferent nitrogenous nutrients labeled with N^{15} leads to the prompt excretion of a large portion of the isotope in the form of urinary uric acid[12] much as the same experiment in mammals leads to the excretion of isotopic urea.

Among the several fates of glycine in man is its contribution in the synthesis of purines.

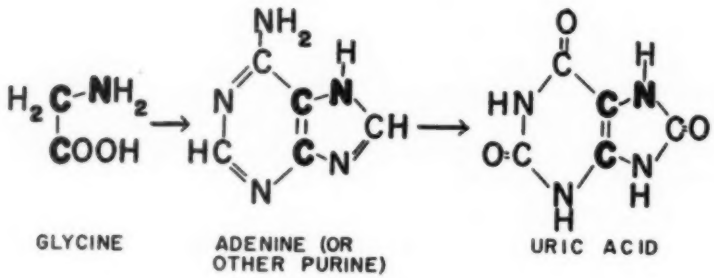

Figure 2

This is apparently a quantitatively minor fate of ingested glycine but it does serve to label the purines of the body when N^{15}-glycine is fed. Purines occur mostly in the nucleic acids and nucleotides, relatively large reservoirs which have been shown to be metabolically sluggish in the adult mammal.[13] A small portion of the purines in these reservoirs is each day mobilized, oxidized to uric acid and excreted.

This reconstruction of events is consistent with what we have observed in experiments on normal man.[14] When isotopic glycine was fed, the N^{15} concentration in urinary uric acid rose slowly to a maximum after three to four days and declined gradually thereafter indicating that isotope was deriving from a large and metabolically sluggish pool of labeled purines. After ten days, whereas from 30 to 50 per cent of the isotope administered had been excreted, chiefly as urea, only about 0.15 per cent had been excreted as uric acid.

In the three gouty subjects who have been studied thus far by this technique, a somewhat different picture is seen. In two of these, the abundance of N^{15} in urinary uric acid rose to a sharp maximum on the second day, and this maximum was about three times as high as that seen in the normal subjects. Successive N^{15} concentrations in the excreted uric acid declined far more rapidly than was seen in the normal subjects, and this decline was reminiscent of what occurs in urea in man and what might be anticipated in urinary uric acid in the bird. In all cases, the fraction of the N^{15} administered as glycine which appeared in urinary uric acid was larger in the gouty than in the normal subjects. Whereas there was no significant deviation from normal in the elimination of isotopic nitrogen as urea, as much as 0.5 per cent of the N^{15} fed as glycine was recovered as urinary uric acid after ten days. This represents a three-fold increase over normal in the incorporation of dietary glycine nitrogen into urinary uric acid.

In one gouty subject, two feedings of identical quantities of isotopic glycine have been carried out.[15] During the first experiment he was on a low-protein diet, during the second, on a high-protein diet. Despite the fact that in the latter experiment the isotope must have sustained a greater alimentary dilution, the concentrations of N^{15} in excreted uric acid were higher at all points in time when a high- rather than when a low-protein diet was fed.

These results considered together indicate that in the gouty subject a fraction larger than normal of dietary glycine is utilized for the synthesis of uric acid which is promptly excreted in the urine. This increased generation of uric acid from dietary nitrogenous precursors, operating over a prolonged period, is adequate to account for the increase in size of the miscible pool of uric acid seen in gout. The deflection of an abnormally large portion of dietary glycine into uric acid synthesis, further exaggerated when the diet is rich in protein, and apparently shortcircuiting the large body reservoirs of purines, is reminiscent of the normal situation in birds and reptiles, and suggests that the metabolic defect in gout may be attributed to an unusually large *urico*telic component in a predominantly *ureo*telic species.

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HALSTED, THE SURGEON'S PRECEPTOR*

JOHN J. MOORHEAD

WILLIAM STEWART HALSTED is one of the immortals in the memory and daily practice of every surgeon. This is a broad statement, but it is entirely true because Halsted's teachings and practices are applicable to any branch of the art and science of surgery even today.

At the time of his death 7 September 1922, aged 70, he had been at Johns Hopkins Hospital since the opening of that institution in 1889, a period of thirty-three years. It is interesting to us in New York to recall that two of the four members of Hopkins (Welch, Osler, Halsted, Kelly) portrayed in the famed painting by Sargent, were originally connected with Bellevue Hospital. Welch was on the Bellevue House Staff, and the first Professor of Pathology at Bellevue Medical College; and Halsted, born in New York City, was not only an intern and subsequently Attending Surgeon at Bellevue, but also Attending at Presbyterian Hospital and Assistant Attending at Roosevelt Hospital. It was in the laboratory of Bellevue Medical College that Welch did his pioneer work on gas gangrene from material furnished him by our own Harlow Brooks[1] who was one of his assistants and then attached to the Pathological Department of Bellevue. A further relationship to our city is noted by the appointment of Dr. Winford H. Smith as Superintendent of Johns Hopkins Hospital when he resigned as Superintendent of Bellevue and Allied Hospitals to go to Baltimore.[1] Dr. Smith had been invited as my guest to a dinner of the New York Post-Graduate Medical School Faculty Association at which William Welch was to be the principal speaker. Dr. Welch called Smith up to the dais early in the evening and made an appointment for the following morning, and shortly thereafter, Hopkins had a new superintendent.

When Halsted underwent an operation for a strangulated umbilical hernia, a New York surgeon was in attendance, assisted by the then youthful John M. T. Finney. A further and final link between Halsted

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and our city occurred when George Heuer, later of Cornell University Medical College, and New York Hospital, operated upon Halsted for gall stones and a postoperative fatal pneumonia occurred. The well known Surgeon John F. Erdmann was House Surgeon at Bellevue during a part of the period Halsted was Attending Surgeon. He told me that Halsted was afraid that his patients would be contaminated by remaining within the hallowed walls of ancient Bellevue, and accordingly he operated for a time in a tent erected within the Hospital grounds. Some of the proletariat might well have referred to it as "Halstead's circus."

In his autobiography published 12 years ago, Finney relates that he was associated with Halsted for 33 years and succeeded him as Professor of Surgery during a three year period and then resigned to provide the successorship for a younger man, Dean Lewis. In the interval, Finney declined the offer to become President of Princeton to succeed Woodrow Wilson. Finney says that Halsted was "An excellent listener. . . . Better writer than speaker, as he was a better surgeon than operator. As an original thinker and investigator interested in the larger problems of scientific surgery, he was without a peer . . . he should be classed as a 'head' surgeon rather than as a 'hand' one. He was much more interested in thinking surgery than in doing it, happier in the laboratory than in the operating room. . . ."

Finney describes the "Professor," as Halsted was called by the irreverent residents, as a very sarcastic individual, rarely given to praise, but eminently just and fair, but not lavish in his friendships, especially by comparison with Osler. The celebrated "big four" Sargent painting is matched by another known as the "all star operation." In this, Halsted is operating surrounded by a group composed of such stalwarts as Cushing, Finney, Bloodgood, Young, and Baetger.

The story of Halsted's advocacy of rubber gloves is phrased by Finney as "Venus came to the aid of Aesculapius." It appears that Miss Caroline Hampton, operating room nurse, was allergic to the carbolic and bichloride solutions used to sterilize the hands and forearms of the operating room staff. Halsted knew that the German surgeon Mikulicz wore cotton gloves when operating but these did not appear to be a suitable protective for Miss Hampton. As an experiment, a rubber gauntlet type of sterilized glove was made for this young lady and this proved so satisfactory that subsequently a thin rubber material was sub-

stituted and thus was created a new item of regalia which became the vogue for the operating crew. Halsted's interest in the operating room nurse was also allergic, soon so apparent that the outcome was inevitable, and Miss Hampton became Mrs. Halsted. Apparently, this set the marital fashion and numbers of the staff married nurses, including Thayer and Finney, and soon Hopkins became known among the nurses, as a sort of pre-nuptial agency. Mrs. Halsted, a strong personality, subsequently was operated on by Finney for appendicitis. He relates that the day after her operation she wanted to get out of bed.* From previous experience he knew better than to forbid this novel expression of self-management, and she won, but fortunately no complications arose. It was another manifestation of what so often happens when the patient is a doctor, a member of the doctor's family, or a nurse. They all get well after behaving most outrageously, or else they develop hydrophobia or the bends, but rarely lockjaw.

I dare say Halsted is best remembered by surgeons because of his insistence on a fixed technique, the use of silk for ligatures and sutures, and the practice of careful hemostasis and asepsis. His contributions to the surgery of breast tumors, inguinal hernia, aneurisms, and local anesthesia will never be forgotten. He could not be classed as a master technician in the sense of his dexterous confrere Kelly who was rapid as well as expeditious. On the contrary, Halsted was by comparison a plodder but his patients nevertheless made an excellent recovery. George Crile[2] in his autobiography says that he and William Mayo once went to see Halsted operate for a tumor of the breast. After an hour or more they left before the operation was well under way, and Crile says he asked Mayo what he thought of the procedure, and the reply was: "Well, that wound will be all healed by the time he gets through sewing up."

Halsted and his group were great teachers and they have trained many men who in turn have trained others so that an ever widening group of competent successors have been recruited to benefit our calling. It is interesting to record an allusion of another prominent surgeon. In 1932 Lord Moynihan,[3] then President of the Royal College of Surgeons of England, in his Romanes Lecture asserted: "It may safely be claimed that the craft of surgery has in these days almost reached the end of its progress along the lines which so far it has followed . . . infection

* An example of voluntary "early ambulation."

may confidently be denied entrance to any fresh wound in which an infective focus is not opened. Operations are consequently performed by the great masters with a success that leaves little hope of betterment. . . ." Moynihan, known to many as one of the most eloquent and skillful surgeons on the continent and a great admirer of American surgery, did not mean that technical surgical progress had reached the end of the trail. On the contrary, his plea was for a correlation of physiology and medicine to the end that the earlier stages of pathological processes might be recognized before actually becoming menacing. His was the doctrine of awareness that we call preventive surgery and medicine; and in perspective, I wonder what Halsted would regard as outstanding, if he today re-entered the surgical world. He was essentially a clinician trained to use his special senses, and he lacked many of the diagnostic aides now so freely employed. One observation that he would promptly make, would be that people are now different in their surgical manifestations. Where are the hunchbacks, the club feet, the crippled joints, the glands of the neck, the varicose ulcers, the grossly infected hands, the empyemas? He saw all these thirty years ago but to our present group of younger men, these once common ailments are now as rare as typhoid or smallpox. And what would he say about this amazing kind of surgery that explores with impunity such closed cavities as the skull, the spinal canal, and the thoracic cage? Again, what of the anesthesia changes, inhalant in type, or local, block or spinal? Greatest of all, perhaps, are the antibiotics, even though too many of the present generation have the idea that these so-called "miracle drugs" are a substitute for the exacting surgery Halsted taught and practiced. Assuredly, he would not approve of publication to the laity of untried remedies for the cure of such scourges as tuberculosis. He had lived and practiced long enough to witness the rise and fall in enthusiasm for this operative procedure, or that form of therapeutics supposedly reliable, until proved to the contrary after more prolonged trial. And he would have given little credence to the assertions of the occasional operator or others of limited knowledge and experience who exploited before they explored.

In one of the surgical fields he cultivated, vascular surgery, he would have been amazed at the progress already made and in prospect. Indeed, he would prophecy that substitution or replacement surgery would supply needed new blood vessels, alter and reverse the blood stream.

More than that, the heart itself would be reconstructed, the valves realigned, and the coronary vessels perhaps rerouted or replaced. Indeed, he might envision the days ahead when a central organ would be transplanted in all its essentials. This anastomosis prospect is fascinating, and not too far distant is the restoration of a kidney or other organ with an accessible blood supply. Blood substitutes, animal or chemical, he would assert are sure to be discovered and processed into concentrated long lasting solid or usable potentials universally applicable. He would be vastly interested in tissue banks where skin, bone, blood vessels and other bodily components were available in sterile containers ready for immediate use. Interested as he always was in suture methods and materials, Halsted recognized that our method of coaptation was almost prehistoric and far behind the practices of prevailing reparative mechanisms. The ancients are said to have had a human glue that coapted even the eyelids or the inside of the cheek, and adequately brought together the huge wounds of the thigh so common among the pyramid builders. Indeed, open fractures of the femur for example in those days were very common, for we know traumatic surgery was one of the very earliest types of surgical endeavor. And adapting alien skin and bone for grafting purposes would be a laboratory enterprise sure to enthuse Halsted and enlist his active support. He would be interested also in the prospect of chemically dissolving calculi in the gall bladder and its ducts, and in the kidney, ureter and bladder. He would promptly and in perspective realize that infections of the appendix, the gall bladder, kidney, pelvic organs and elsewhere could often be controlled by non-operative methods.

And from a diagnostic standpoint, he would recognize the need for a universal electrically operated portable device that would register certain abnormalities in subsurface organs. The heart and brain are thus responsive, and assuredly it should be possible to devise a mechanism that would reliably inform us regarding abnormal processes in the lung, stomach, liver, spleen and elsewhere.

The greatest problem of all, the major culprit, that assassin, cancer, who has eluded us, disdained us and defied us, is still at large, and takes a stealthy staggering toll in every walk of life. This, despite the best efforts of the enlightened throughout the world, who have been on the trail for decades and decades. All of the many devices to entrap this criminal have failed, and indeed we do not know the habitat,

the lineaments, the designs or the origins of this, our greatest foe. When present, we are uncertain as to whether or not we are dealing with a local manifestation of a general disease or are fortunate enough to be attacking only an initial lesion. However, the sustained attack will one day be successful, and to the discoverer of the cause and cure of this scourge, the entire world will give deserved acclaim beyond that ever accorded to any conqueror since the advent of the Saviour of mankind.

And having surveyed the status of the surgery with which he once was familiar, what will our returning visitor say about pre- and post-graduate medical education? For example, does he still favor the whole time professorships, or does he agree with his notable confreres Osler and Finney, who in their lifetime were opposed to this plan? Has he any opinion about government subsidy and control of medical colleges and medical practice? We would like to know what his beliefs are regarding the curriculum for the degree of doctor of medicine, and also as to compulsory post-graduate training. We must tell him that there is in prospect a radio and television type of graduate medical education that gives enticing promise. A special channel will be allotted for this teaching program for which the doctor thousands of miles distant from Johns Hopkins will pay a nominal fee. He will lower the window shade in his office or home at 9 p.m. and listen to the Halsteds, the Oslers, the Welchs and the Kellys of 1952 and thus find himself attuned to the galaxy of medical stars of his own choosing. However, at the broadcasting studio there will be no performers paid $2500 for each appearance, nor will there be any commercials to take away the advertising from medical journals. Or will there be? Gone will be the days of the amphitheatre in the graduate medical school because the matriculants are now receiving aerial delivery instruction long after graduation. There will be a consultation service in which a practitioner can tune in some authority who will actually examine the patient and have almost as direct contact as if seated at the bedside. And there will be a loaning library for the surgeon who wants a repeat recording of an already televised operation by a recognized expert. This will be portrayed the night before the viewing surgeon is to operate on an identical case. Thus the vicarious value of this kind of education is almost unlimited for the graduate of medicine, and of course for undergraduates the same procedure seems alluring.

Canned medical education is on the march, Dr. Halsted, and per-

haps the faculty of the medical college of the future will consist mainly of the television operator, a secretary and a janitor.

Thus in outline we have sketched the career of this surgical personage, and mentioned some of his outstanding contributions to the art and science of surgery. We have brought the "professor" back in imagination to hear his opinion of present day surgery a century after his birth, and have ventured to answer for him some of our own queries. Realizing that it is unusual for any surgeon to be honored on the centennial year of his birth, we are glad to bear tribute to one who has advanced the teaching and practice of his calling.

He is indeed another representative of the precept: "If every man would mend a man, then all the world were mended."

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NEW YORK PATHOLOGICAL SOCIETY

Abstracts of Papers

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The Use of the Radioautographic Technique in Pathology

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Radioautography is a simple, inexpensive, reliable technique which seems to have been made to order for the morphologist. With it one may localize extremely small amounts of radioactive isotopes to histologic structures, cells, or even to intracellular structures. Even individual tracks of alpha or beta particles emitted by an atom may be recognized. The technique preserves histology so that the structural features of normal organs, growth processes, or pathologic changes may be correlated with isotope localization. The recent advances in labeling of compounds by the chemist and physicist indicate that practically all substances involved in biology—carbohydrates, fats, proteins, hormones, steroids, and others—may be made radioactive.

Using labeled compounds, the radioautographic technique, and judicious experimentation, one might readily map the metabolic journey of many compounds from ingestion to excretion by pinpointing the structural organ highways through which they may hurry or any cytologic inns wherein they might tarry. Thus the old boundaries between morphology and function become less conspicuous and phenomena may be described in terms of both disciplines.

The present atomic era had its origin in an accidental radioautograph and the curiosity of a physicist, when Becquerel developed the photographic film upon which uranium salts had been resting in his desk. The discovery of an image on the photographic film led to the discovery of natural radioactivity and its momentous sequelae. Lacassagne was the first to make significant application of the technique in biology. He used blocks of tissue from animals who had been given polonium and obtained images on photographic emulsions of those organs containing the isotope. Of recent years there have been great advances in technique and photographic emulsions so that intracellular localization is possible with many isotopes.

The technique makes use of photographic emulsions to record an image of radioactive areas in contiguous areas of animals, organs, histologic sections, cells, or other objects. The alpha and beta particles, and, occasionally, the gamma rays, emitted by the radioactive isotope reduce the grains of silver bromide in the photographic emulsion just as visible light does in photography. In some methods the specimen is removed from the emulsion when the latter is developed and processed. In others, a histologic section may be floated in a water bath, picked up on a piece of x-ray film, or on a glass plate covered with emulsion, dried, deparaffinized, and exposed for days or weeks. The tissue and emulsion are not separated,

the preparation is put through photographic processing to develop the image given by the isotope and the section may be stained. Thus the morphologist may examine the preparation through the visible light microscope focusing on either the tissue or the underlying photographic emulsion to determine if areas of radioactivity in the tissue section had been fingerprinted in the emulsion. Histologic sections or objects may be coated with fluid emulsion or covered with a strip of film emulsion. Each method has peculiar advantages and disadvantages that fit it for particular problems.

Applications

Clinical application of radioautography has been most extensively used in diseases of the thyroid gland. Our material comprises over 250 cases. We studied 100 consecutive cases of carcinoma of the thyroid with radioiodine (I^{131}) and demonstrated evidence of radioactivity in forty-six cases. However, only in one type, alveolar and follicular carcinoma, was there significant concentration of the isotope. In general, those lesions containing considerable colloid were more likely to concentrate radioiodine but the presence of colloid was no guarantee of retention. Thyrotoxicosis showed considerable concentration. Nodular goiter showed variation even throughout the same lesion. Hyperplastic areas were less likely to concentrate the isotope than normal or microfollicular zones. Chronic thyroiditis showed relatively little concentration of isotope. Even after radiation of the thyrotoxic gland with subsequent fibrosis there was intense concentration of radioiodine in the few remaining follicles of these lesions. Radioautographs of these lesions were shown.

Alpha particle radioautography was illustrated by the next case. A patient was given Thorotrast twenty years ago and this past year at operation a biopsy of his liver was taken. Radioautograph shows alpha particle tracks coming from the Thorotrast granules in the cirrhotic liver. Hoecker recently used radioautography to demonstrate alpha particles coming from the Haversian systems of the bones from the original radium watch dial painters. Levi is doing similar work in Denmark with alpha particles from patients given Thorotrast.

As one phase of the Sloan-Kettering Institute nucleic acid studies, killer and sensitive paramecia were grown in media containing C^{14}-labeled adenine, guanine, and 2.6, diaminopurine. These and other studies with glycine, formate, methionine, and acetate, labeled with C^{14}, and methionine, labeled with $sulfur^{35}$, showed that paramecia absorbed these substances and gave these radioautographs.

Kidney antigens known to produce glomerulonephritis were presumed to concentrate in the glomeruli. The immunologists labeled antibodies to these kidney antigens with $sulfur^{35}$ and gave them to mice. The radioautograph shows unquestioned glomerular localization.

Endocrinologists labeled pituitary hormones with I^{131} and injected them into animals. Radioactivity was found in many organs. Of interest to us was the localization of the I^{131} in the proximal convoluted tubules of the kidney even when the original substance labeled was growth hormone, insulin, serum albumin, prolactin, and others. The slide showed that glomerular localization was not present in these animals when blood-radioactivity was negligible.

Current interest in the treatment of carcinomatosis by injection of radiogold into the pleural or peritoneal cavities raised a question as to the concentration of the isotope in the reticuloendothelial system. In rats given gold intraperitoneally, the radioautograph stripping film reveals radioactivity concentrated most heavily in the colloidal gold particles in the cytoplasm of the Kupffer cells of the liver and in the abdominal lymph nodes.

These radioautographs demonstrated that mouse sarcoma cells grown in tissue culture with C^{14}-labeled adenine added to the medium show radioactivity. In a few cells intranuclear concentration can be seen.

In order to improve the resolution of radioautographs we have used tritium, the radioactive isotope of hydrogen, since its energy is so low that it can reduce only one grain of photographic emulsion. Localization of tritium to the cytoplasm of the yeast cells was shown in a slide. Endoplas-

mic and ectoplasmic concentrations of tritium in paramecia were also shown. This is the first time that tritium has been used for radioautography.

Quantitative measurement of both alpha and beta particle radioautographs has been performed by many authors. Accuracy is fair for both methods but with beta particle measurement problems of obtaining accurate standards and densitometry considerations still need considerable study. The slide showed the emulsion response in density versus the logarithm of the intensity of radioactivity of Strontium 90 of various emulsions. It is apparent that the readily available x-ray film is still the most sensitive emulsion although its resolution is poor. The next slide showed the response of nuclear track emulsion to tritium (hydrogen^3). The response is linear.

The next two slides showed the same tissue section of human thyroid gland from a patient who was given radioiodine. The first slide, a radioautograph, shows concentration of radioiodine in small follicles while the large central follicle contains relatively little isotope. The next slide showed the same tissue section which was examined by the x-ray absorption method. Soft x-rays were used to determine the mass or dry weight of tissue without destroying histologic detail. From this slide the colloid of the central follicle is seen to have the greater mass. The smaller follicles containing more radioiodine actually weigh much less. Using this combination of methods with the development of quantitative radioautography the isotopes might be expressed in terms of microcuries per gram of cytologic structure. The combination of radioautography with mass determination by x-ray absorption should add information pertinent to many biological problems.

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DISCUSSION

ALFRED ANGRIST: I should like to ask about the problem of quantitation of uptake. My own experience is limited to P^{32}, and the difficulty in depending on radioautography per se with such variables as the vascularity, and such indefinite features as the porosity or the cancellous nature of a particular portion of bone, all of which will also determine what the uptake will be on a physico-chemical basis, and take priority over many other biological features and of local metabolism, and again too technical features of self-absorption and closeness of apposition, depending on variations in thickness, not only of the local tissue, but the emulsion film—all of these make the problem of quantitation in radioautography less controlled, as Dr. Fitzgerald has so well intimated.

The other point I would like to mention, which I hoped Dr. Fitzgerald would stress, is the possibility of this technique as a new approach for gauging *variations* in local metabolic types of biological activity, once an over-all average is established, as for the epiphyseal site, or for the thyroid, per se, i.e., to see how various stimuli alter that average. That I think will be a great help (and I would be interested to hear his viewpoint in this regard), because it concerns the pathologist particularly, and his getting into this competitive field with the biochemist and physiologist.

PATRICK J. FITZGERALD: I can see that Dr. Angrist has had some experience in this field: he knows the difficulties. P^{32} is not a soft beta emitter—having an energy of about 1.6 Mev—in contrast to C^{14} which is about 0.1 Mev, or tritium (H^3) which is about 0.01 Mev. The problem of quantitation is difficult. The ideal way to do quantitative radioautography is to develop three or four standards of the nature of a plastic in which one can distribute the isotopes uniformly, embed them in the same block with tissue, cut both together and place them on the emulsion. The standards give varying degrees of darkening of the film from which one may draw his curve of response of the film to intensity. Areas of darkening in the radioautograph are measured by den-

sitometry and the measured density interpreted from the curve in units of isotope intensity. We have tried such techniques with many plastics but none really successfully. Dudley from M.I.T. has done some excellent work on this problem and has developed good standards for use with P^{32}. Monomolecular layers of stearates labeled with C^{14} are also a possibility and are being investigated.

One may obtain relatively quantitative values without much trouble. The film emulsions are well standardized at present and although some development of techniques is still necessary there is no reason why there should not be in the near future means for the quantitative analysis of most isotopes.

For the finest work grain counts are probably necessary to determine the amount of isotope present in cells and intracellular structures. Although grain counts are still the most accurate way of doing quantitative work, they are very tedious. I have suggested the use of the new RCA television microscope for grain counts and in a preliminary trial found that the method is quite promising where there is no clumping of grains.

In regard to the physiologic aspects and comparison of the function of different areas, I think that it is extremely important, as Dr. Angrist suggests. One obvious use, and a practical one, is in the field of radiation dosimetry. The concentration of the glomerular antigen in the kidney previously shown increases the local concentration of isotope by a factor of at least thirty as compared to non-glomerular tissue. Thus Geiger-Mueller counting of a gross kidney specimen would lead to an error by that factor when calculating glomerular concentration because uniform distribution, in lieu of radioautographic findings, would have to be assumed. Other applications are apparent—they are legion.

Vascularity is, of course, a factor. One has to wait until blood activity is absent if he is to use gross apposition methods or else use stripping film and grain counting techniques which differentiate cellular from vascular activity.

William Newman: Are there other artefacts in radioautography, such as diffusion, which are encountered in other histochemical attempts at localization, as for example, in enzyme localization?

Patrick J. Fitzgerald: I would say yes, but again it depends on what one is studying. If one is investigating the uptake of P^{32} in the ribonucleic acid fraction, the ordinary fixation and dehydration presumably are not going to disturb this too much. The P^{32} in phospholipids would probably be dissolved by such histologic processing, and the P^{32} in phosphate would certainly be lost. Some studies have to be made with frozen tissues or frozen dehydrated specimens. We know we lost some I^{131} in our thyroid studies as evidenced by Geiger-Mueller counting of the processing fluids. Actually the loss was less than 5 per cent because the isotope had been administered to patients 24 to 48 hours before biopsy and therefore was probably organic bound. If we had taken the specimen minutes after the administration of the isotope histologic processing might have dissolved out a great percentage of the I^{131} as it might not have been bound to protein, and therefore soluble.

One has to beware of these pitfalls in the preparation of the specimen and one also has to know something about the chemical combination of the label in the specimen so as to avoid dissolving it or causing artefacts during some phase of the technical processing. Not infrequently when first approaching a problem we empirically use frozen tissue and compare it with routinely processed tissue for intensity of respective radioautographs. If there is no significant difference then we use the ordinary fixation and processing techniques.

Infantile Testicular Tumors

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A study of twenty-four infantile testicular tumors in the files of the Armed Forces Institute of Pathology revealed that such tumors fall into three main categories. The first consisted of two cases in which the diagnosis was uncertain; the second of seven cases which were classed as teratomas, and the third of fifteen cases considered embryonal carcinomas.

In two cases, areas of spindle-shaped cells alternated with and sometimes surrounded polygonal cells arranged in pseudoalveolar fashion. The cytoplasm of the cells was finely vacuolated, and the tumor had the appearance of a carcinosarcoma. Despite the histologically malignant appearance of the tumor one of the patients is living and well 2½ years, and the other, seven years after operation. The exact diagnosis of these two tumors is unknown, but it is believed that they are possibly interstitial cell tumors.

In seven cases the tumor was classified as belonging to the so-called adult teratoma group, with various mature or immature somatic elements occurring in a haphazard fashion and occasionally simulating primitive or abortive organ formation. No deaths have been reported in this group, but follow-up has been inadequate.

The tumors in the remaining fifteen cases were regarded as embryonal carcinoma, with glands and acini alternating with cellular areas in which the cells were vacuolated or fenestrated. Some of the vacuoles contained fat, but many of them seemed to coalesce to form larger spaces, some empty, others containing cellular debris. These tumors appeared to have an affinity for blood vessels and in a number of cases they were seen in vascular spaces. In seven of the tumors of this group structures suggesting primitive somatic elements were observed, and areas suggestive of chorionic elements were present in three.

It is believed that the 15 tumors in the third group are derived from early trophoblastic elements in contrast to the tumors of the second group which are derived from early somatic elements of the immature sex cell.

It is of interest that no seminomas were observed in this series of infantile testicular tumors.

DISCUSSION

MEYER M. MELICOW: I would like briefly to discuss tumors of the testis in infants from four aspects:

Their congenital nature. The majority seem to occur before the third year, and in many of the more recent reports the ages ranged from birth to the seventh or eighth month, although occasionally the patient was not seen before the third or fifth year. It does seem that testicular tumors in infants, particularly the embryonal carcinomas, are of congenital nature.

2. *Their relation to undescended testes.* Tumors of the testis in adults are said to be more common in patients with undescended testes and some authors report a twenty-five to fifty times greater incidence. There is some doubt as to the correctness of these estimates. We have no adequate statistics of the incidence of undescended testis and of the incidence of tumor in such testes as compared with those in the normally placed organ. Recently Carroll sent a questionnaire to over 640 urologists and more than 500 replied that they had never encountered a tumor in an undescended testis. We have seen two patients at the Columbia-Presbyterian Medical Center in whom a tumor developed in the descended testis and none in the undescended. During the last World War we missed a great opportunity to investigate adequately this problem while ex-

amining inductees and volunteers. No statistics on this subject were accumulated, yet within a few years the Army Institute of Pathology report on over 900 cases of testicular tumors. As to infants, no mention is made in most reports as to whether the neoplasm developed in an abnormally placed testis.

3. *Their relation to testis tumors in the adult.* Dr. Mostofi mentioned that there were no seminomas in his group. We have been impressed by this fact: apparently seminomas do not develop in infants. We have no time tonight to attempt to give an explanation for this interesting phenomenon.

4. *Their classification.* The slide shows our classification of tumors of the testis. In classifying tumors of any organ, one should consider its components and in the testis we have, besides the blood vessels, connective tissue, fat, etc., (which can form their own tumors): (a) Sertoli cells, (b) Leydig cells, and (c) spermatogones and their derivatives.

a) Tumors of the Sertoli cells are feminizing and have not been encountered in children. (Hoffman's case with gynecomastia may have been one.)

b) Tumors of the interstitial cell produce precocious pseudopuberty and about 10 cases, including one from our files, have been reported. The majority developed symptoms at about the 5th year. Our case, a five year old boy, had symptoms for five months. The picture shows a boy 126 cm. tall and weighing 31,500 grams. His voice was rough, his genitalia were enlarged. He had pubic hair and in general presented the picture of macrogenitosomia. The close-up shows the large penis and the scrotal mass. The boy was operated upon and a large tumor involving the right testis was removed. Kodachromes show the gross tumor and the microscopic sections. Note the large interstitial cells with eccentric nuclei and prominent nucleoli. The group of patients presented a uniform syndrome. It is of interest to note that the very meager follow-up indicated that post-operative recession in most cases was negligible. Our patient too is still of his age, both as to sex and somatic development. Why interstitial cell tumors should cause precocious sexual development in children and feminization in adults is a paradox and a curiosity. We do know of the work of Gardner, Hooker, Bonser et al who induced interstitial cell tumors in immature male rats by injections of estrogens. We see an increase in interstitial cells in adult males with liver damage. These patients often have large breasts, sparse hair and loss of libido. They show an excess of estrogens. Could it be that the tumors in children are a counter response to some profound estrogenic influence?

Dr. Mostofi's two cases of interstitial cell tumors are interesting. He did not state whether an endocrine disturbance was present. The interstitial cells after birth do degenerate and become spindle-shaped although the sections he has shown, particularly because of the accompanying gland-like structures, resemble the so-called mesotheliomas or adenomatoid tumors.

c) The remaining tumors, by far the largest number, arise from some toti-potent cell (a spermatocyte) or, according to some, from an imported wandering germ cell that settled in the testis and finally became activated. They constitute a complex group and are difficult to classify. They take in the embryomas, trophoblastomas, teratocarcinomas and adult teratomas. I wonder if Dr. Mostofi means that all his fifteen cases of embryonal carcinoma had trophoblast elements, or only some.

We have seen only one case of an embryonal carcinoma. The slides from the eighteen months old infant were shown to us by Dr. Lattes.

Dorothy H. Andersen: I feel that we have little to add to Dr. Mostofi's experience. We cannot go back, as he can, to 1863, but only to 1921, and we have only the experience of a small hospital, rather than of the United States Army, to draw on; this makes an obvious difference in our statistics. In the files of the Babies' Hospital since 1921, which is the point at which I started the index of diagnosis, there are listed the following tumors of the testis: one tumor before my time which looks in the photograph like an embryonal carcinoma; we have had one tumor which we called a lymphosarcoma (?); we have had

one which was composed of mixed mesodermal tissues and which may have arisen either from the testis or the scrotum. In addition to these we have had two hemangiomas, one tumor reported as an adrenal rest, twelve leukemic infiltrations or nodules, and four other miscellaneous metastatic tumors. Over the past thirty years in our hospital we have had a limited experience, really too little to contribute much. We can say that tumors of the testis in childhood are rare, and therefore they are always a puzzle when they present themselves. We are grateful to Dr. Mostofi for bringing us his more extensive material which will enable us to deal more adequately with our future problems in this field.

PETER GRUENWALD: I have seen one testis tumor in an infant. This was a testis which contained renal glomeruli and tubules, apparently through some kind of tissue malformation, and developed a typical Wilms' tumor. I do not think it would fit into any classification.

JOHN M. PEARCE: The interstitial cell tumors which Dr. Mostofi showed are quite different from those which Dr. Melicow showed. We have seen the type which Dr. Melicow showed. Would Dr. Mostofi care to comment on this?

F. K. MOSTOFI: I wish to thank Dr. Melicow and Dr. Andersen for their kind comments.

I should emphasize that I really do not know the diagnosis of the tumor observed in the two cases making up the first group. Three alternatives may be considered: one, that they are Wilms' tumors, as suggested by Dr. Gruenwald. When the first of these tumors was examined the impression was that it was possibly Wilms' tumor. When the second one came to our notice, with wet tissue and paraffin blocks available so that the tumor could be studied more thoroughly, the usual primitive nephroblastic elements and other characteristics of a true Wilms' tumor were not present. The biologic behavior of the tumor was also unlike that of Wilms' which usually causes death within the first year or two.

As to the second possibility—that suggested by Dr. Melicow—all I can say is that in contrast to testicular adenomatoid tumors in an extratesticular location, these 2 tumors were in the substance of the testes, and were morphologically unlike 50 or 60 adenomatoid tumors that I have studied.

The third possibility is that these may be interstitial cell tumors. You will recall that the interstitial cells of the infant *in utero* and during the first few days of life are polygonal. After the first week or two of extra-uterine life they become spindle-shaped. At this age they are indistinguishable from the stromal cells. Later they become polygonal and assume the characteristic appearance. It was this potentiality of the interstitial cell, that is, its ability to change from spindle-shaped to polygonal, that led me to suggest the possibility of an interstitial cell tumor. Another factor favoring this diagnosis is the increased cellularity of the seminiferous tubules in the uninvolved portions of the testes. In these areas the stromal cells were indistinguishable from the tumor cells. Perhaps the term stromal tumor is preferable to interstitial tumor, but that is what I thought they might be. This is the group that has been variously designated as androblastoma, Sertoli cell tumor,[1] and theca granulosa cell tumor of the testis, but the tumor cells certainly do not resemble Sertoli cells and there is no evidence of estrogen production if one can rely on the morphologic characteristics of the uninvolved testis to indicate estrogen effects.

The correlation of this group with the tumor described by Dr. Melicow is very difficult. I do not know how to explain this discrepancy; perhaps it is due to the different stages in the tumor's evolution, and that if the two tumors had been allowed to remain they would have assumed an appearance similar to Dr. Melicow's tumor. I must emphasize, though, that the diagnosis of possible interstitial cell tumor is entirely provisional. These rare hormone-producing testicular tumors, i.e., interstitial cell tumors and Sertoli cell tumors, are baffling and need clinico-pathologic investigation, with preoperative hormone determinations and hormone assays on the tumor. It would be

of interest to know the status of the pituitary and adrenals in these patients.

I agree with Dr. Melicow that most of the tumors are congenital. None of the infants had undescended testes. All were in the scrotum. In only three of the patients in the embryonal carcinoma group did I see structures which I thought were chorionic elements. In the others, the vacuoles, the fenestration, and the relationship to the blood vessels suggested that the tumors possessed some of the potentialities of the primitive trophoblastic tissue. This is, of course, a theory and cannot be proved, and therefore these tumors were called embryonal carcinomas rather than choriocarcinomas.

Dr. Andersen's case of lymphoma in the testes of an infant is of great interest. Although several lymphomas of the testes have been seen at the Armed Forces Institute of Pathology, none have been in infants. Absence of seminoma in the twenty-four cases that I have studied may be due to the fact that such cases have not been sent to us for consultation. But since Dr. Andersen and Dr. Melicow have likewise seen no cases of seminoma in infants and since none have been seen in the Children's Hospital in Boston, it may be presumed that seminomas do not exist in infants.

I wish to thank you again for the privilege of being with you.

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Notice

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MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

Beginning with November 1952, the Academy, under the auspices of the Committee on Medical Education, will present each month, from November to April inclusive, a panel discussion on therapeutics.

This series will replace the Friday Afternoon Lectures Series and will deal with the practical and specific problems which confront the practising physician.

The following subjects will be presented for the panel meetings, to be held on Friday afternoon at 4:30 o'clock:

November 7, 1952	MANAGEMENT OF DIABETES *Moderator* — George E. Anderson
December 5, 1952	HEPATITIS AND CIRRHOSIS OF THE LIVER *Moderator* — Franklin M. Hanger
January 9, 1953	HYPERTENSIVE VASCULAR DISEASES *Moderator* — William Goldring
February 6, 1953	DISORDERS OF THE BLOOD *Moderator* — Claude E. Forkner
March 6, 1953	THE FAILING HEART *Moderator* — Charles E. Kossmann
April 3, 1953	RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS *Moderator* — Charles Ragan

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EVENING LECTURE PROGRAM

MONDAY, OCTOBER 6

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HORMONES AND COMMON SENSE
LUDWIG KAST AWARD
FULLER ALBRIGHT, *Associate Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital*

HORMONES OF THE ANTERIOR PITUITARY GLAND
ABRAHAM WHITE, PH.D., *Lecturer in Biochemistry, College of Physicians and Surgeons, Columbia University*

THE REGULATION OF WATER EXCRETION BY THE NEUROHYPOPHYSIS
H. B. VAN DYKE, *Hosack Professor of Pharmacology, College of Physicians and Surgeons, Columbia University*

TUESDAY, OCTOBER 7

HORMONES OF THE ADRENAL CORTEX
E. C. KENDALL, PH.D., *The James Forrestal Research Center, Princeton University*

DIAGNOSIS OF ENDOCRINE DISEASE: CLINICAL AND LABORATORY CONSIDERATIONS
LOUIS J. SOFFER, *Associate Attending Physician and Head of Department of Endocrinology, The Mount Sinai Hospital, New York*

WEDNESDAY, OCTOBER 8

THE ENDOCRINE CONTROL OF METABOLISM
FRANK L. ENGEL, *Associate Professor of Medicine and Associate in Physiology, Duke University*

DISTURBANCES IN GROWTH
LAWSON WILKINS, *Associate Professor of Pediatrics, Johns Hopkins Medical School; Director of Endocrine Clinic, Harriet Lane Home, Baltimore*

THURSDAY, OCTOBER 9

MANAGEMENT OF ADDISON'S DISEASE IN ADRENALECTOMIZED PATIENTS
D. M. BERGENSTAL, *Assistant Professor of Medicine, University of Chicago Medical School*

ACTH, CORTISONE AND RELATED STEROIDS IN CLINICAL MEDICINE: PRACTICAL CONSIDERATIONS
CHARLES RAGAN, *Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University*

FRIDAY, OCTOBER 10

PHEOCHROMOCYTOMA WITHIN AND WITHOUT THE ADRENAL MEDULLA
GEORGE F. CAHILL, *Professor of Urology, College of Physicians and Surgeons, Columbia University; Director of Department of Urology, Presbyterian and Francis Delafield Hospitals*

VIRILISM
JOSEPH W. JAILER, *Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital*

MONDAY, OCTOBER 13

CUSHING'S SYNDROME

ABBIE I. KNOWLTON, *Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University*

DIABETES: METABOLIC EFFECTS OF INSULIN

DEWITT STETTEN, JR., *Chief, Division of Nutrition and Physiology, The Public Health Research Institute of The City of New York, Inc.*

TUESDAY, OCTOBER 14

THE PITUITARY THYROID RELATIONSHIP IN NORMAL AND DISORDERED THYROID STATES

SIDNEY C. WERNER, *Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital*

CHOICE OF MANAGEMENT IN HYPERTHYROIDISM

CYRUS C. STURGIS, *Professor and Chairman of the Department of Internal Medicine; Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan*

WEDNESDAY, OCTOBER 15

THYROIDITIS AND MYXEDEMA

CARPENTER LECTURE

DAVID P. BARR, *Professor of Medicine, Cornell University Medical College; Physician-in-Chief, The New York Hospital*

PARATHYROIDS AND CALCIUM METABOLISM

I. SNAPPER, *Physician and Director of Medical Education of The Mount Sinai Hospital, New York*

THURSDAY, OCTOBER 16

USE OF THE STEROIDS AND GONADOTROPINS IN GYNECOLOGY

HOWARD C. TAYLOR, JR., *Professor of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University; Director of Obstetrics and Gynecology, Sloane Hospital of the Columbia-Presbyterian Medical Center*

HORMONAL CONTROL OF NEOPLASTIC GROWTH

RULON W. RAWSON, *Attending Physician, Memorial Hospital; Chief, Division of Clinical Investigation, Sloan-Kettering Institute; Professor of Medicine, Sloan-Kettering Division, Cornell University Medical College*

FRIDAY, OCTOBER 17

THE RELATIONSHIP OF HORMONES TO PEPTIC ULCER

JOSEPH B. KIRSNER, *Professor of Medicine, University of Chicago*

HORMONES AND THEIR INFLUENCE ON THE EMOTIONS

FRANCIS J. BRACELAND, *Psychiatrist-in-Chief, Institute of Living; Clinical Professor of Psychiatry, Yale University*

MORNING PANEL PROGRAM

Wednesday, October 8

PRACTICAL CONSIDERATIONS REGARDING REALISM AND WISHFUL THINKING IN ENDOCRINE THERAPY

Chairman: RUSTIN MCINTOSH

Friday, October 10

PRACTICAL CONSIDERATIONS REGARDING THE USE OF ACTH AND CORTISONE

Chairman: LOUIS LEITER

Wednesday, October 15

PRACTICAL CONSIDERATIONS REGARDING DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN DISORDERS OF THE THYROID GLAND

Chairman: DAVID P. BARR

Friday, October 17

PRACTICAL CONSIDERATIONS REGARDING HORMONAL MANAGEMENT OF MALIGNANT NEOPLASMS

Chairman: C. P. RHOADS

HOSPITAL CLINICS PROGRAM

All Clinics will be held from 2 to 5 P.M.

CALENDAR OF CLINICS

First Week

Monday, October 6

1. Bellevue
   Hospital Representative: CHARLES F. WILKINSON, JR.
2. Montefiore
   Hospital Representative: SAMUEL M. SEIDLIN

Tuesday, October 7

3. New York
   Hospital Representative: EPHRAIM SHORR
4. Flower-Fifth Avenue
   Hospital Representative: CLAIR E. FOLSOME

Wednesday, October 8

5. University
   Hospital Representative: LOCKE L. MACKENZIE
6. Veterans Administration
   Hospital Representative: BERNARD STRAUS

Thursday, October 9

7. Presbyterian
   Hospital Representative: JOSEPH W. JAILER
8. Morrisania
   Hospital Representative: EDWARD P. FLOOD

Friday, October 10

9. Mount Sinai
   Hospital Representative: LOUIS J. SOFFER
10. Bellevue
    Hospital Representative: CHARLES F. WILKINSON, JR.

Second Week

Monday, October 13

11. Mount Sinai
    Hospital Representative: SOLOMON SILVER
12. Beth Israel
    Hospital Representative: ARTHUR M. FISHBERG

Tuesday, October 14

13. New York
    Hospital Representative: EPHRAIM SHORR
14. Montefiore
    Hospital Representative: SAMUEL M. SEIDLIN

Wednesday, October 15

15. Roosevelt
    Hospital Representative: JOHN E. HUTTON
16. Polyclinic
    Hospital Representative: JAMES P. CROCE

Thursday, October 16

17. Presbyterian
    Hospital Representative: JOSEPH W. JAILER
18. St. Luke's
    Hospital Representative: WILLIAM NORTON, II

Friday, October 17

19. Harlem
    Hospital Representative: ALEXANDER ALTSCHUL
20. Memorial
    Hospital Representative: RULON W. RAWSON

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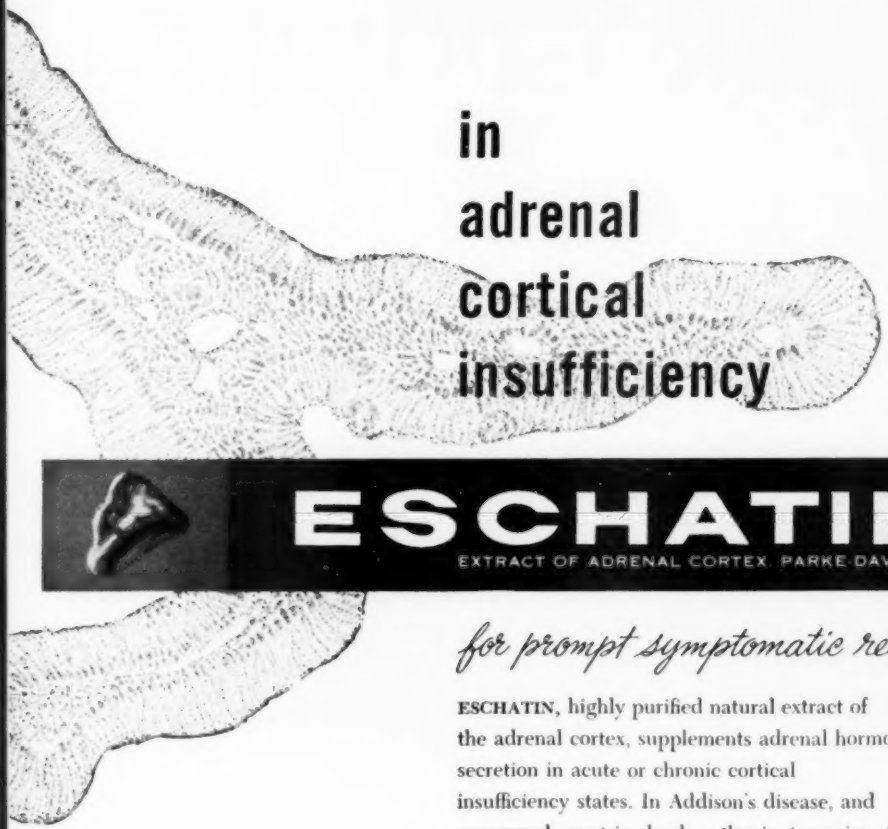

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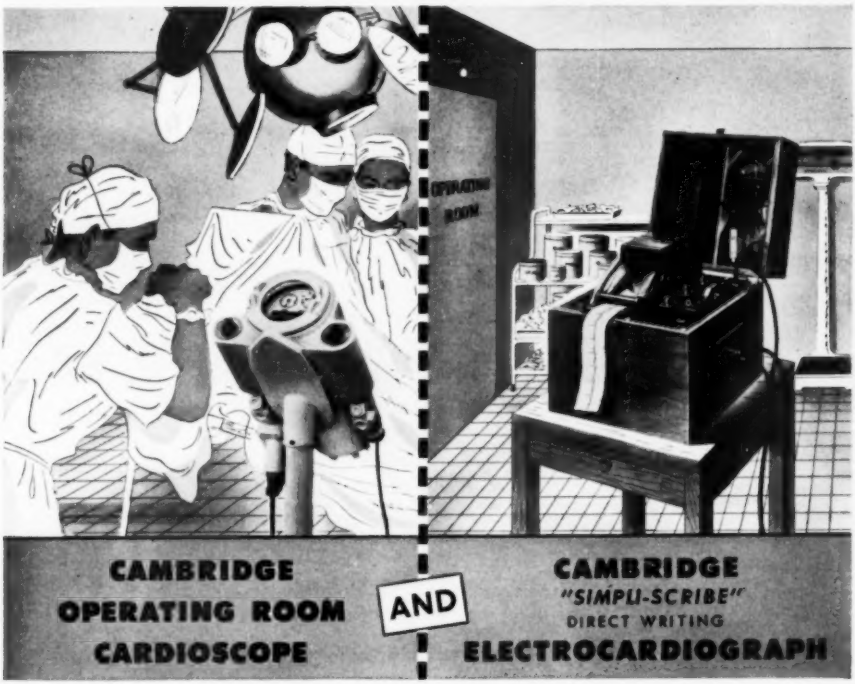

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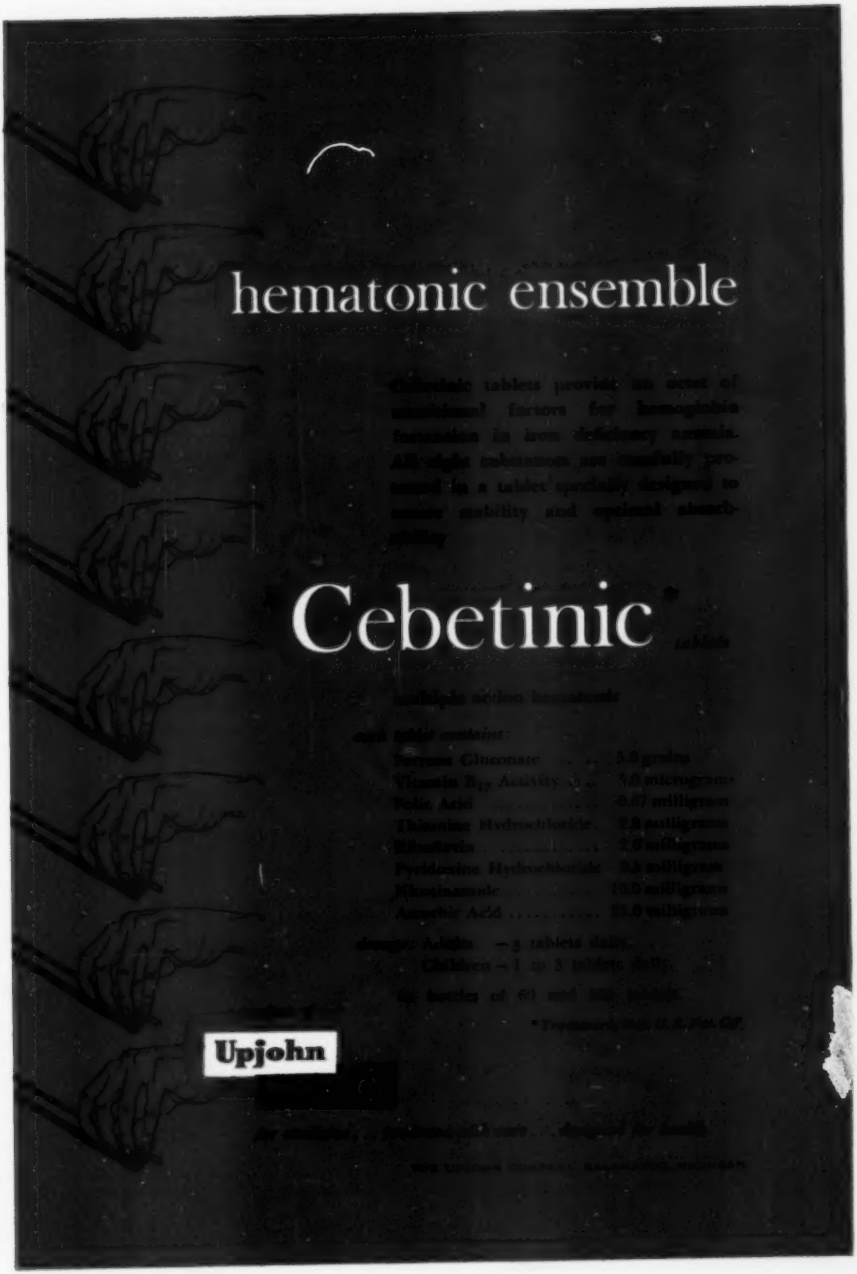
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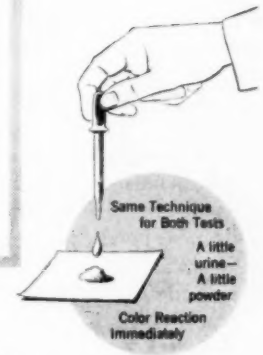

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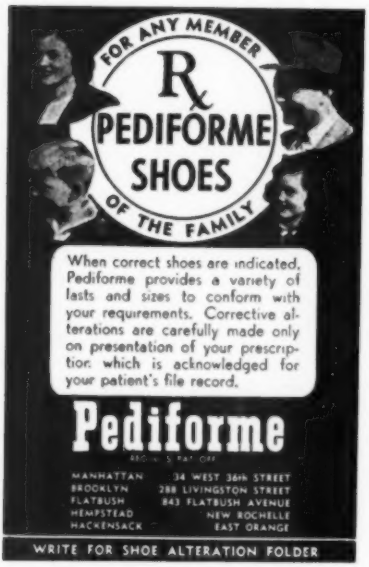
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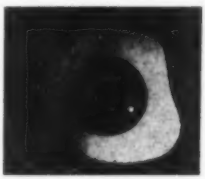

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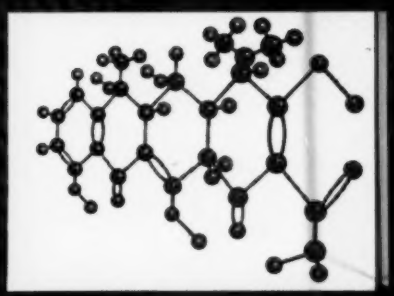

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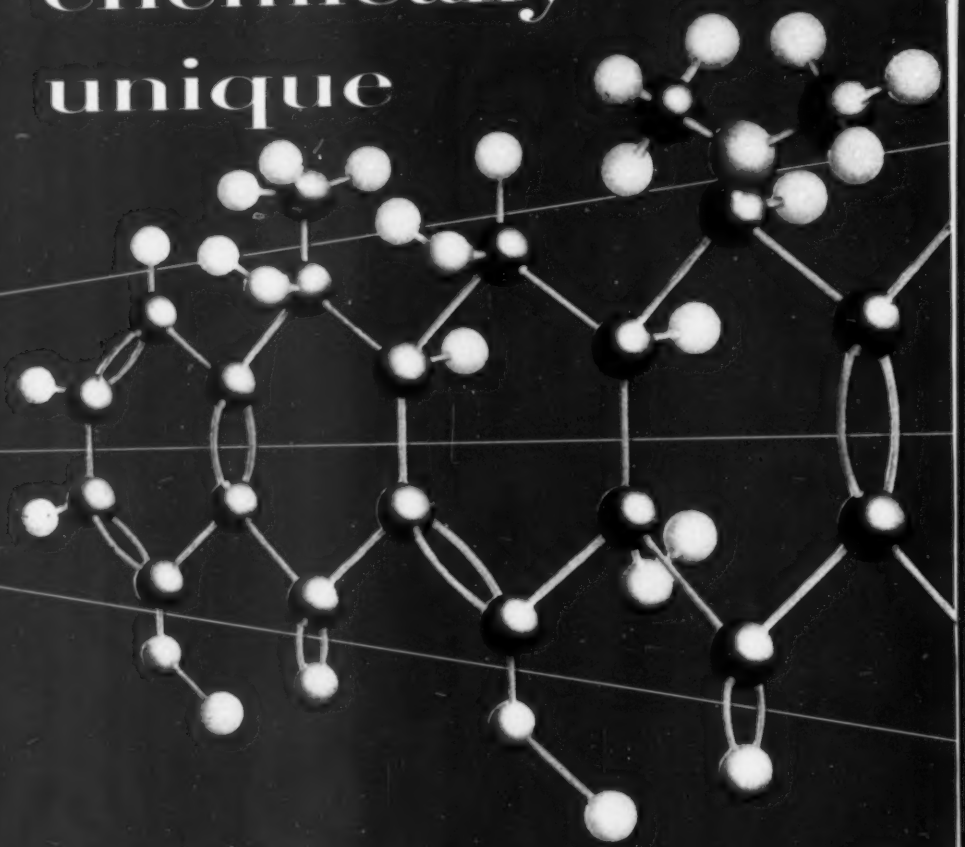

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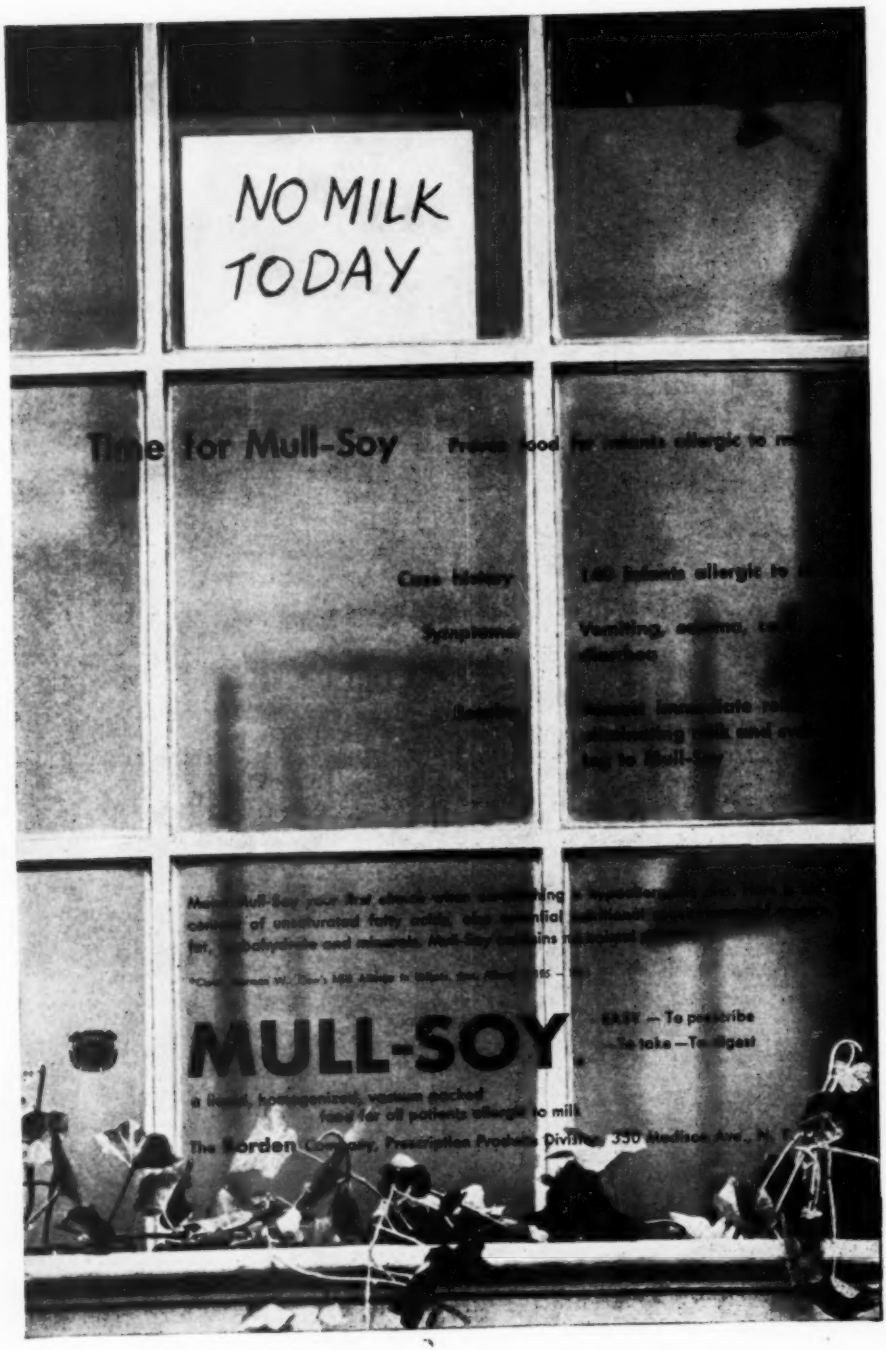
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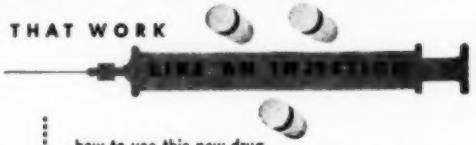

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